Thieno[2,3-c]pyrroles: Synthesis, Diels-Alder Reaction, and Synthetic Utility

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5*H*-Thieno[2,3-*c*]pyrrole **1a** and the N-substituted derivatives **1b–h** and **11–13** were synthesized by the novel retro-malonate addition reaction. Thieno[2,3-*c*]pyrroles readily underwent the Diels–Alder reaction with reactive dienophiles, such as *N*-phenylmaleimide or dimethyl acetylenedicarboxylate. Extrusion of the imine nitrogen from the Diels–Alder adduct **16b** produced benzo[*b*]thiophene **20**. The free-energy barriers of inversion of the imine nitrogens of the cycloadducts **16** were investigated by variable-temperature ^{1}H NMR spectroscopy.

Thienopyrroles **1**, consisting of two heterocyclic five-membered rings with six π-electrons, are of interest from both a theoretical[1] and a synthetic[2] point of view. They are also of potential pharmaceutical importance because they are isosteric with indoles.[3] Furthermore, the development of the synthesis of electroconducting polymers based on heteroaromatic monomers has stimulated a search for the efficient synthesis for the thiophene and the pyrrole derivatives.[4] Recently, in our preliminary communications, we described the first synthesis 5*H*-thieno[2,3-*c*]pyrrole **1a**[5] and the preparation of some N-substituted derivatives **1b–f**.[6] In this paper, we report the synthesis of thieno[2,3-*c*]pyrroles in some detail and their Diels–Alder reaction as well as the synthesis benzo[*b*]thiophene **20** from the Diels–Alder adducts **16**. In addition, we also present the investigation of the free-energy barriers of inversion of the imino nitrogens of the Diels–Alder adducts **16** by variable-temperature ^{1}H NMR spectroscopy.

Results and Discussion

Synthesis of Thieno[2,3-*c*]pyrroles. Knoevenagel condensation of 3-methyl-2-thiophenecarboxaldehyde (**2**) with diethyl malonate gave **3**. Bromination of **3** with *N*-bromosuccinimide and dibenzoyl peroxide afforded bromide **4**. Bromide **4** was treated with sodium azide in ethanol to give the azido compound **5**. Treatment of **5** with triphenylphosphine follow by water afforded the parent compound 5*H*-thieno[2,3-*c*]pyrrole (**1a**).[5] Alternatively, direct reaction of bromide **4** with ammonia also afforded the parent compound **1a** in 30% yield. Furthermore, reaction of bromide **4** with primary amines such as methylamine, isopropylamine, *tert*-butylamine, benzylamine, aniline, or cyclohexylamine gave the N-substituted thieno[2,3-*c*]pyrroles **1b–g** in excellent yields.[6] A proposed mechanism is shown in Scheme I. Methyl glycinate also reacted smoothly with **4** to give N-substituted thieno[2,3-*c*]pyrrole **1h**. Furthermore, treatment of **4** with 0.5 equiv of ethylenediamine led to the formation of two thieno[2,3-*c*]pyrrole rings on the same substrate to give the novel bis[thieno[2,3-*c*]pyrrole] derivative **11**. Treatment of **4** with triethylamine and 1 equiv of 1,4-phenylenediamine gave compound **12**. Thieno[2,3-*c*]pyrrole derivative **12** was then treated with **4** and triethylamine to afford the new compound **13**, Scheme II. In order to convert the parent compound **1a** into a stable derivative, compound **1a** was treated with di-*tert*-butyl dicarbonate and 4-(dimethylamino)pyridine to give the more stable *N*-*tert*-butoxycarbonyl derivative **1i**.

Diels–Alder Reaction of Thieno[2,3-*c*]pyrroles and Synthesis of Benzo[*b*]thiophene. With thieno[2,3-*c*]pyrroles **1a–i** in hand, we decided to study the Diels–Alder reactions of **1a–i** with common dienophiles. We found that thieno[2,3-*c*]pyrroles **1** react readily in a Diels–Alder reaction with reactive dienophiles such as *N*-phenylmaleimide and dimethyl acetylenedicarboxylate but does not react with the less reactive dienophile such as methyl acrylate and dimethyl maleate at 80 °C. The Diels–Alder reaction of the parent compound **1a** with *N*-phenylmaleimide occurred at room temperature to give the endo adduct **14a** (4%) and exo adduct **15a** (39%), Scheme III. To follow the reaction closely, the reaction of *N*-methylthieno[2,3-*c*]pyrrole **1b** with *N*-phenylmaleimide was monitored by ^{1}H NMR spectroscopy. A ^{1}H NMR spectrum obtained immediately after mixing **1b** with 10 equiv of *N*-phenylmaleimide suggested the almost exclusive formation of the endo adduct **14b** (95%). However, the endo adduct **14b** would slowly equilibrate to the exo adduct **15b** at room temperature. On the other hand, cycloaddition of **1b–i** with 1–1.3 equiv of dimethyl acetylenedicarboxylate (DMAD) gave the cycloadducts **16b–i** in excellent yields. Either the addition of the second equivalent of DMAD to **16b** or the reaction of **1b** with 2.4 equiv of DMAD directly gave a mixture of 2:1 adducts **17** and **18**.[7]

At this point, we envisioned that extrusion of the imine nitrogen from the Diels–Alder adducts **16b–i** would lead to the benzo[*b*]thiophene ring system.[8] Thus, cycloadduct **16b** was oxidized with *m*-chloroperbenzoic acid and then thermolyzed to give benzo[*b*]thiophene **20**,[9] scheme IV.

Free-Energy Barrier of Inversion of the Imine Nitrogen. The ^{1}H NMR spectra of Diels–Alder adducts **16b–i** were usually broad at room temperature, which appears to be due to the slow inversion of the nitrogen atom of the imine bridge. For this reason we conducted ^{1}H NMR experiments at temperatures in the range of −50 to 50 °C. The coalescence temperature (T_C) for compounds **16b–f** were determined. The corresponding free-energy barriers of inversion were calculated.[10] The ratios

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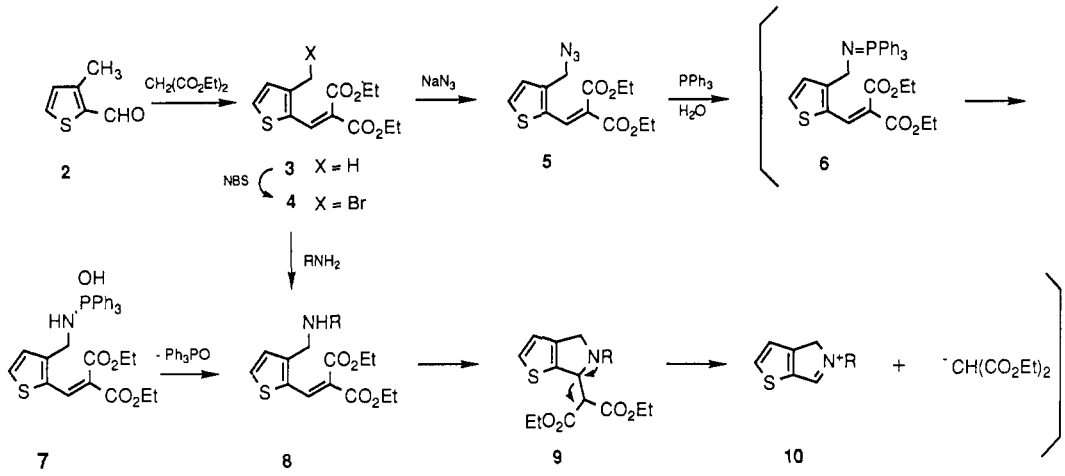
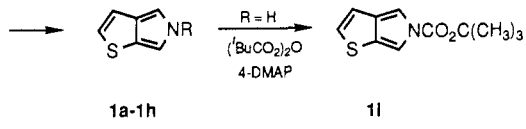
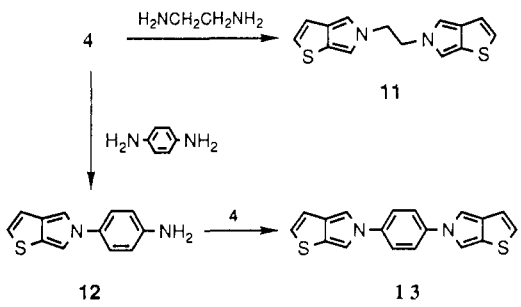
Scheme I



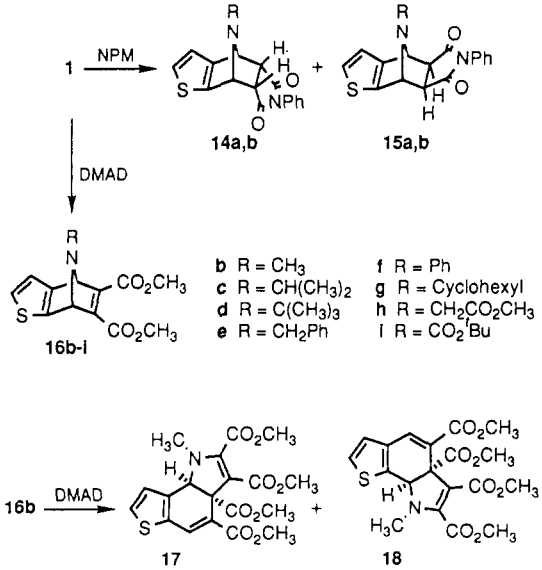


1a R = H
b R = CH_3
c R = $CH(CH_3)_2$
d R = $C(CH_3)_3$
e R = CH_2Ph
f R = Ph
g R = Cyclohexyl
h R = $CH_2CO_2CH_3$

Scheme II



Scheme III



b R = CH_3 f R = Ph
c R = $CH(CH_3)_2$ g R = Cyclohexyl
d R = $C(CH_3)_3$ h R = $CH_2CO_2CH_3$
e R = CH_2Ph i R = $CO_2{}^tBu$

of invertomers at −50 °C were estimated from the ^1H NMR peak areas. Only the *tert*-butyl derivative **16d** clearly favors one invertomer over the second (62:38 at −55 °C), Table I. It is interesting to note that T_C of the *tert*-butyl-substituted compound **16d** is −50 °C, much lower than that for the isopropyl-substituted compound **16c**. This large difference in T_C has been attributed to the steric effect.[11] On the other hand, the coalescence temperature T_C of phenyl-substituted compound **16f** is below −50 °C, which is presumably due to the resonance of the lone-pair electrons on nitrogen with the benzene π-electrons.[12]

Scheme IV

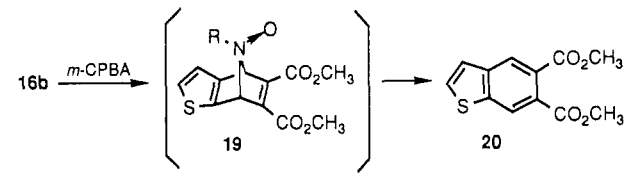
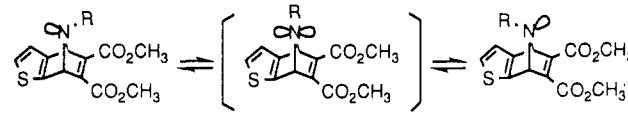


Table I. The Free-Energy Barrier of Inversion of the Nitrogen Substituents of 16



compound	T_c,[a] °C	K_c,[b] s^{-1}	ΔG,[c] kcal/mol	ratio of invertomers at −50 °C
16b, R = CH_3	27	210	14.4	50:50
16c, R = $CH(CH_3)_2$	22	338	13.8	50:50
16d, R = $C(CH_3)_3$	−50	197	10.6	62:38
16e, R = CH_2Ph	23	246	14.1	57:43
16f, R = Ph	<−50			

[a] T_c = coalescence temperature for nitrogen. [b] k_c = rate constant at T_c; $k_c = 2.22\Delta\delta$. [c] ΔG = free energy of activation for nitrogen inversion; $\Delta G = 0.00457T_c(9.97 + \log T_c/\Delta\delta)$ kcal/mol.

Conclusion

In summary, a general and expeditious method for the synthesis of thieno[2,3-c]pyrroles has been developed. While similar reactions of 2-(bromomethyl)thiophenecarboxaldehyde with amines could also give the same

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products, in general these aldehydes are not readily available. Thus, bromide **4** serves as the synthetic equivalent of (bromomethyl)thiophenecarboxaldehyde. Because this methodology is experimentally simple and efficient, it should allow the preparation of thieno[2,3-*c*]pyrroles on a large scale. Furthermore, the Diels–Alder reaction of thieno[2,3-*c*]pyrroles followed by the removal of the imine nitrogen from the cycloadducts constitutes a new entry to the benzo[*b*]thiophene ring system.

Experimental Section

General. Melting points were determined with a Yanaco micro melting point apparatus. ^{1}H NMR spectra were recorded on a Varian EM-390, a JEOL HX-100, or a Bruker AM-400 spectrometer. ^{13}C NMR spectra were recorded in a JEOL HX-100 or a Bruker AM-400 spectrometer. Mass spectra refer to the electron-impact mass spectra and were recorded on a JEOL TMS-D-100 mass spectrometer. High-resolution mass spectra were taken on a JEOL HX-110 mass spectrometer. IR spectra were recorded on a Perkin-Elmer 781 spectrometer, and UV spectra were recorded on a Perkin-Elmer Lambda 5 UV–vis spectrometer. Solvents were distilled before use and were dried, as necessary, according to literature procedures. All reactions were conducted under a nitrogen atmosphere. Elemental analyses were performed by the Microanalytical Laboratory of the NSC Regional Instrumentation Center operated by Department of Chemistry, National Cheng Kung University, Tainan, Taiwan.

Diethyl [(3-Methyl-2-thienyl)methylene]propanedioate (3). To a solution of 3-methyl-2-thiophenecarboxaldehyde (**2**) (3.78 g, 30 mmol) in benzene (120 mL) was added diethyl malonate (7.20 g, 45 mmol), piperidine (0.3 mL), and acetic acid (0.2 mL). The reaction mixture was refluxed for 20 h with a Dean–Stark water separator attached. After cooling, the solution was washed with water, sodium carbonate solution, and brine. Concentration and recrystallization (5% ethyl acetate in hexane) gave **3** (7.40 g, 92%) as white crystals: mp 67–68 °C; IR (KBr) 3100, 2980, 1725, 1715, 1605 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.98 (s, 1 H), 7.38 (d, 1 H, J = 5.5 Hz), 6.87 (d, 1 H, J = 5.5 Hz), 4.38 (q, 2 H, J = 7.5 Hz), 4.28 (q, 2 H, J = 7.5 Hz), 2.28 (s, 3 H), 1.35 (t, 3 H, J = 7.5 Hz), 1.26 (t, 3 H, J = 7.5 Hz); ^{13}C NMR (25.1 MHz, $CDCl_3$) δ 166.1 (s), 164.2 (s), 144.2 (s), 132.3 (d), 130.1 (d), 130.0 (s), 129.6 (d), 121.4 (s), 61.6 (t), 61.3 (t), 14.4 (q), 14.2 (q), 13.9 (q); MS m/z (relative intensity) 268 (M$^+$, 100), 222 (60), 178 (31), 150 (58). Anal. Calcd for $C_{13}H_{16}O_4S$: C, 58.19; H, 6.01; S, 11.95. Found: C, 58.48; H, 6.11; S, 12.18.

Diethyl [[3-(Bromomethyl)-2-thienyl]methylene]propanedioate (4). To a solution of **3** (2.68 g, 10 mmol) in carbon tetrachloride (100 mL) was added *N*-bromosuccinimide (2.12 g, 12 mmol) and dibenzoyl peroxide (0.05 g). The reaction mixture was stirred and heated at refluxed for 5 h. After the mixture was cooled in an ice bath, the solid was removed by filtration and washed with carbon tetrachloride. The combined filtrate was concentrated to give an oily residue. Silica gel flash column chromatography (hexane–ethyl acetate, 6:1) gave **4** (2.96 g, 85%) as white crystals: mp 58–59 °C, IR (KBr) 3100, 3000–2900, 1725, 1710, 1610 cm^{-1}; ^{1}H NMR (90 MHz, CCl_4) δ 7.77 (s, 1 H), 7.34 (d, 1 H, J = 5.5 Hz), 7.02 (d, 1 H, J = 5.5 Hz), 4.52 (s, 2 H), 4.28 (q, 2 H, J = 8.0 Hz), 4.25 (q, 2 H, J = 8.0 Hz), 1.31 (t, 6 H, J = 8.0 Hz); ^{13}C NMR (25.1 MHz, $CDCl_3$) δ 165.4 (s), 163.4 (s), 142.2 (s), 132.2 (s), 130.1 (d), 129.9 (d), 129.2 (d), 123.2 (s), 61.6 (t), 61.4 (t), 24.5 (t), 13.9 (q), 13.7 (q); MS m/z (relative intensity) 348 (M$^+$ + 2, 22), 346 (M$^+$, 22), 267 (100), 221 (61), 193 (83). Anal. Calcd for $C_{13}H_{15}BrO_4S$: C, 44.97; H, 4.35; Br, 23.01; S, 9.23. Found: C, 45.40; H, 4.45; Br, 23.06; S, 9.46.

Diethyl [[3-(Azidomethyl)-2-thienyl]methylene]propanedioate (5). To a solution of **4** (347 mg, 1 mmol) in 95% ethanol (20 mL) was added sodium azide (130 mg, 2 mmol). The reaction mixture was stirred at room temperature for 2 h. The solution was concentrated to remove ethanol, and the residue was taken up in ether. The ether solution was washed with water and brine and then dried ($MgSO_4$). Concentration and silica gel flash column chromatography (hexane–ethyl acetate, 5:1) gave **5** (303 mg, 98%) as a yellow oil: IR (neat) 3120, 3000–2880, 2110, 1735, 1625 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.88 (s, 1 H), 7.49 (d, 1 H, J = 5.5 Hz), 7.09 (d, 1 H, J = 5.5 Hz), 4.47 (s, 2 H), 4.39 (q, 2 H, J = 7.5 Hz), 4.30 (q, 2 H, J = 7.5 Hz), 1.37 (t, 3 H, J = 7.5 Hz), 1.30 (t, 3 H, J = 7.5 Hz); ^{13}C NMR (25.1 MHz, $CDCl_3$) δ 165.4 (s), 163.5 (s), 140.5 (s), 132.3 (s), 130.4 (d), 130.1 (d), 128.7 (d), 123.6 (s), 61.7 (t), 61.4 (t), 47.1 (t), 13.9 (q), 13.7 (q) ; MS m/z (relative intensity) 309 (M$^+$, 33), 281 (M$^+$ – 28, 50), 208 (100), 186 (50), 162 (92). Anal. Calcd for $C_{13}H_{15}N_3O_4S$: C, 50.48; H, 4.89; N, 13.58; S, 10.36. Found: C, 50.45; H, 4.84; N, 13.56; S, 10.16.

5*H*-Thieno[2,3-*c*]pyrrole (1a).[5] To a solution of **5** (650 mg, 2.1 mmol) in dry tetrahydrofuran (20 mL) was added triphenylphosphine (640 mg, 2.4 mmol). The reaction mixture was stirred at room temperature for 3 h. Water (1 mL) was then added, and the mixture was stirred for 18 h. Concentration and silica gel flash column chromatography (hexane–ethyl acetate, 6:1) gave **1a** (217 mg, 78%) as colorless crystals, which could be stored at –20 °C under nitrogen: mp 68.5–69.5 °C; IR (KBr) 3400, 3100, 3080, 1575 cm^{-1}; UV (EtOH) λ_{max} 285 (ϵ 7.35 × 10^3), 230 (ϵ 1.34 × 10^4) nm; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.7 (br s, 1 H, NH), 7.06 (br s, 1 H), 6.97 and 6.91 (AB q, 2 H, J = 5.3 Hz), 6.95 (br s, 1 H). ^{13}C NMR (100.6 MHz, acetone-d_6) δ 133.13 (s), 125.93 (d), 124.14 (s), 116.76 (d), 107.15 (d), 106.97 (d); MS m/z (relative intensity) 123 (M$^+$, 100); HRMS calcd for C_6H_5NS 123.0144, found 123.0129.

General Procedure for the Synthesis of N-Substituted Thieno[2,3-*c*]pyrroles 1a–h. To a solution of ammonia or a primary amine (3–15 mmol) in 95% ethanol (5 mL) was added a solution of **4** (1 mmol) in 95% ethanol (15 mL). The reaction mixture was stirred at room temperature and at reflux for 0.5–24 h.[6] Concentration and silica gel flash column chromatography (hexane–ethyl acetate) gave **1a–h**.

***N*-Methylthieno[2,3-*c*]pyrrole (1b).** To a 40% aqueous solution of methylamine (1.163 g, 15 mmol) was added 95% ethanol (5 mL), and then dropwise a solution of **4** (347 mg, 1 mmol) in 95% ethanol (15 mL). The reaction mixture was stirred at room temperature for 1 h. Concentration and silica gel flash column chromatography (hexane–ethyl acetate, 12:1) gave **1b** (112 mg, 82%) as a yellow oil: IR (neat) 3120, 2930, 1570 cm^{-1}; UV (CH_2Cl_2) λ_{max} 286 (ϵ 6.24 × 10^3), 239 (ϵ 8.38 × 10^3) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96, 6.95, 6.94, and 6.92 (AB q, 2 H), 6.86 (d, 1 H, J = 1.84 Hz), 6.74 (d, 1 H, J = 1.76 Hz), 3.84 (s, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 132.31 (s), 125.04 (d), 123.68 (s), 115.64 (d), 110.27 (d), 110.10 (d), 37.04 (q); MS m/z (relative intensity) 137 (M$^+$, 100); HRMS calcd for C_7H_7NS 137.0299, found 137.0289.

Methyl [5-Thieno[2,3-*c*]pyrrolyl]acetate (1h). A solution of methyl glycinate (3 mmol) was prepared by addition of methyl glycinate hydrochloride (374 mg) to a solution of triethylamine (303 mg) in 95% ethanol (5 mL). To this solution was added a solution of **9** (347 mg, 1 mmol) in 95% ethanol (15 mL). The reaction mixture was stirred at room temperature for 6 h. Concentration and silica gel flash column chromatography (hexane–ethyl acetate, 6:1) gave **1h** (137 mg, 70%) as a yellow oil: IR (KBr) 3140, 2960, 1750, 1575 cm^{-1}; UV (CH_2Cl_2) λ_{max} 287 (ϵ 9.53 × 10^3), 235 (ϵ 1.92 × 10^4) nm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, 1 H, J = 5.52 Hz), 6.89–6.87 (m, 2 H), 6.76 (d, 1 H, J = 1.44 Hz), 4.76 (s, 2 H), 3.75 (s, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.72 (s), 132.97 (s), 126.23 (d), 124.62 (s), 115.75 (d), 110.50 (d), 110.44 (d), 52.53 (t), 51.79 (q); MS m/z (relative intensity) 195 (M$^+$, 100); HRMS calcd for $C_9H_9NO_2S$ 195.0354, found 195.0352.

***N*-(*tert*-Butoxycarbonyl)thieno[2,3-*c*]pyrrole (1i).** To a solution of **1a** (31 mg, 0.25 mmol) in dichloromethane (5 mL) was added 4-(dimethylamino)pyridine (61 mg, 0.5 mmol) and a solution of di-*tert*-butyl dicarbonate (164 mg, 0.75 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 1 h. Concentration and silica gel flash column chromatography (hexane–ethyl acetate, 12:1) gave **1i** (45 mg, 81%) as white crystals: mp 131–132 °C; IR ($CHCl_3$) 2985–2935, 2870, 1742 cm^{-1}; UV (CH_2Cl_2) λ_{max} 315 (ϵ 2.54 × 10^3); ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.42 (d, 1 H, J = 2.0 Hz), 7.33 (d, 1 H, J = 2.0 Hz), 7.00 (d, 1 H, J = 5.4 Hz), 6.81 (d, 1 H, J = 5.4 Hz), 1.62 (s, 9 H); MS m/z (relative intensity) 223 (71, M$^+$), 167 (100), 123 (57); HRMS calcd for $C_{11}H_{13}O_2S$ 223.0668, found 223.0680.

1,2-Bis[5-thieno[2,3-*c*]pyrrolyl]ethane (11). To a solution of ethylenediamine (30 mg, 0.5 mmol) and triethylamine (303 mg, 3 mmol) in 95% ethanol (5 mL) was added a solution of **4** (347 mg, 1 mmol) in 95% ethanol (15 mL) dropwise. The reaction mixture was stirred at room temperature for 2.5 h. Concentration and silica gel flash column chromatography (hexane–ethyl acetate,

6:1) gave **11** (27 mg, 10%) as white crystals: mp 172–173 °C dec; IR (KBr) 3125, 3070, 2940, 1567, 1500 cm^{-1}; UV (CH_2Cl_2) λ_{max} 286 (ϵ 8.60 × 10^3), 235 (ϵ 1.81 × 10^4) nm; ^1H NMR (90 MHz, $CDCl_3$) δ 6.92 and 6.80 (AB q, 4 H, J = 5.2 Hz), 6.63 (d, 2 H, J = 1.6 Hz), 6.54 (d, 2 H, J = 1.6 Hz), 4.33 (s, 4 H); MS m/z (relative intensity) 272 (M^+, 100); HRMS calcd for $C_{14}H_{12}N_2S_2$ 272.0442, found 272.0435.

5-(*p*-Aminophenyl)thieno[2,3-*c*]pyrrole (12). To a solution of 1,4-phenylenediamine (108 mg, 1 mmol) and triethylamine (101 mg, 1 mmol) in 95% ethanol (5 mL) was added a solution of **4** (174 mg, 0.5 mmol) in 95% ethanol (5 mL) dropwise. The reaction mixture was stirred at room temperature for 2 h, and then refluxed for 2 h. Concentration and silica gel flash column chromatography (hexane–ethyl acetate, 4:1) gave **12** (55 mg, 51%) as yellow crystals: mp 125–127 °C; IR (KBr) 3390, 3330, 3140, 1620, 1520 cm^{-1}; UV (CH_2Cl_2) λ_{max} 264 (ϵ 4.11 × 10^4), 227 (ϵ 1.83 × 10^4) nm; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24–7.21 (m, 2 H), 7.14 (d, 1 H, J = 1.72 Hz), 7.04 (d, 1 H, J = 1.64 Hz), 6.95, 6.94, 6.93, and 6.92 (AB q, 2 H) 6.73–6.71 (m, 2 H), 3.72 (br s, 2 H, NH_2); MS m/z (relative intensity) 214 (M^+, 100); HRMS calcd for $C_{12}H_{10}N_2S$ 214.0565, found 214.0568.

1,4-Bis[5-thieno[2,3-*c*]pyrrolyl]benzene (13). To a solution of **12** (40 mg, 0.19 mmol) and triethylamine (51 mg, 0.50 mmol) in 95% ethanol (1 mL) was added a solution of **4** (58 mg, 0.17 mmol) in 95% ethanol (3 mL) dropwise. The reaction mixture was stirred at room temperature for 1 h and then refluxed for 12 h. After the mixture was cooled to room temperature, the product was precipitated. Filtration and washing with cold ethanol gave **13** (33 mg, 55%) as a white solid: mp 295–300 °C dec; IR (KBr) 3145, 1540, 1530 cm^{-1}; UV (EtOH) λ_{max} 299 (ϵ 1.9 × 10^4), 268 (ϵ 2.0 × 10^4), 206 (ϵ 2.1 × 10^4) nm; ^1H NMR (400 MHz, DMSO-d_6) δ 7.78 (s, 4 H), 7.68 (d, 2 H, J = 1.72 Hz), 7.64 (br s, 2 H), 7.17 (d, 2 H, J = 5.20 Hz), 6.99 (d, 2 H, J = 5.24 Hz); MS m/z (relative intensity) 320 (M^+, 100); HRMS calcd for $C_{18}H_{12}N_2S_2$ 320.0437, found 320.0422.

***endo*- and *exo*-*N*-Phenyl-4,5,6,7-tetrahydrobenzo[*b*]thiophen-4,7-imine-5,6-dicarboximide (14a and 15a).** To a solution of **1a** (47 mg, 0.38 mmol) in tetrahydrofuran (10 mL) was added *N*-phenylmaleimide (73 mg, 0.42 mmol). The reaction mixture was stirred at room temperature for 12 h. Concentration and silica gel flash column chromatography (hexane–ethyl acetate, 3:1) gave the endo adduct **14a** (4.5 mg, 4%) as white crystals (mp 233–235 °C dec), and the exo adduct **15a** (43.3 mg, 39%) as white crystals (mp 173–175 °C dec). Data for the endo adduct **14a**: IR (KBr) 3480, 3040, 1780, 1740–1710, 1595 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) at 20 °C δ 7.53–7.42 (m, 3 H), 7.32 (d, 1 H, J = 4.8 Hz), 7.29–7.26 (m, 2 H), 7.03 (d, 1 H, J = 4.8 Hz), 5.97, 5.94, 5.91, 5.87 (4 s, 2 H), 3.11, 3.06 (AB q, 2 H, J = 6.9 Hz), 1.61 (br s, 1 H, NH); 296 M^+, 15), 187 (53), 185 (100), 173 (18), 123 (15). Data for the exo adduct **15a**: IR (KBr) 3300, 1770, 1705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) at 21 °C δ 7.49–7.29 (m, 5 H), 7.24 (d, 1 H, J = 4.6 Hz), 6.91 (d, 1 H, J = 4.6 Hz), 5.04 (s, 1 H), 4.97 (s, 1 H), 2.88 (d, 1 H, J = 6.8 Hz), 2.85 (d, 1 H, J = 6.8 Hz), 1.67 (br s, 1 H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.93 (s), 175.63 (s), 155.20 (s), 149.51 (s), 131.97 (s), 129.78 (d), 129.11 (d), 128.65 (d), 126.53 (d), 119.03 (d), 63.44 (d), 62.83 (d), 49.81 (d), 49.56 (d); MS m/z (relative intensity) 296 (M^+, 10), 173 (55), 123 (100); HRMS calcd for $C_{16}H_{12}N_2O_2S$ 296.0620, found 296, 0614.

***endo*- and *exo*-*N*-Phenyl-4,5,6,7-tetrahydro-8-methylbenzo[*b*]thiophen-4,7-imine-5,6-dicarboximide (14b and 15b). Method A: Using the Ether–Hexane Solvent System.** To a solution of **1b** in a mixture of ether and hexane (2:1, 4 mL) was added *N*-phenylmaleimide (141 mg, 0.82 mmol). The reaction mixture was stirred at room temperature for 10 h. The product that precipitated as white crystals was filtered. The crystals were washed with a mixture of ether and hexane (1:3) and dried in vacuo to give only the endo adduct **14b** (152 mg, 78%): mp 82.5–83.5 °C; IR (KBr) 3090, 2963, 2860, 2795, 1770, 1720–1695, 1598 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) at 21 °C δ 7.34–7.28 (m, 4 H), 6.96 (d, 1 H, J = 4.6 Hz), 6.72–6.70 (m, 2 H), 4.73 (d, 1 H, J = 4.6 Hz), 4.65 (d, 1 H, J = 4.6 Hz), 3.91–3.86 (m, 2 H), 2.27 (s, 3 H); MS m/z (relative intensity) 173 (M^+ – 137, 20), 137 (M^+ – 173, 100). Anal. Calcd for $C_{17}H_{14}N_2O_2S$: C, 65.79; H, 4.55; N, 9.03. Found: C, 65.66; H, 4.58; N, 9.02.

Method B: Using Benzene as the Solvent. To a solution of **1b** (100 mg, 0.73 mmol) in benzene (10 mL) was added *N*-phenylmaleimide (162 mg, 0.94 mmol). The reaction mixture was stirred at room temperature for 7 days. Concentration and silica gel flash column chromatography (hexane–ethyl acetate, 4:1) gave the exo adduct **15b** (165 mg, 73%) as white crystals, and only trace of the endo adduct **14b** (eluted with hexane–ethyl acetate, 1:1). The endo adduct **14b** was unstable to silica gel chromatography. Data for the exo adduct **15b**: mp 152.5–154.5 °C; IR (KBr) 3100, 3070, 2960, 2845, 2793, 1775, 1730–1690, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48–7.23 (m, 6 H), 6.93 (d, 1 H, J = 4.6 Hz), 4.62 (s, 1 H), 4.53 (s, 1 H), 2.89 and 2.85 (AB q, 2 H, J = 6.8 Hz) 2.20 (s, 3 H); MS m/z (relative intensity) 173 (M^+ – 137, 55), 137 (M^+ – 173, 100). Anal. Calcd for $C_{17}H_{14}N_2O_2S$: C, 65.79; H, 4.55; N, 9.03. Found: C, 65.70; H, 4.62; N, 9.01.

Dimethyl 4,7-Dihydro-8-methylbenzo[*b*]thiophen-4,7-imine-5,6-dicarboxylate (16b). To a solution of **1b** (137 mg, 1 mmol) in benzene (10 mL) was added dimethyl acetylenedicarboxylate (DMAD) (142 mg, 1 mmol). The reaction mixture was stirred at room temperature for 4 h. Concentration and silica gel flash column chromatography (hexane–ethyl acetate, 3:1) gave **16b** (267 mg, 92%) as a yellow oil. Spectral data indicated the presence of two invertomers: IR (neat) 3100–3080, 3000, 2950, 2865, 2790, 1740–1710, 1633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) at 50 °C δ 7.24–6.95 (m, 2 H), 4.95 (s, 1 H), 4.92 (s, 1 H), 3.75 (s, 6 H), 2.33 (br s, 3 H); ^1H NMR (400 MHz, $CDCl_3$) at –50 °C showed two sets of peaks δ 7.02 (br s, 1 H), 7.01 (d, 0.5 H, J = 4.5 Hz), 6.91 (d, 0.5 H, J = 1.8 Hz), 5.05 (d, 0.5 H, J = 1.4 Hz), 4.98 (d, 0.5 H, J = 1.8 Hz), 4.97 (d, 0.5 Hz, J = 2.1 Hz), 4.89 (d, 0.5 H, J = 1.3 Hz), 3.76 (s, 3 H), 3.75 (s, 3 H), 2.48 (s, 1.5 H), 2.24 (s, 1.5 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) at –50 °C δ 164.70 (s), 164.47 (s), 163.36 (s), 163.13 (s), 155.44 (s), 154.09 (s) 153.77 (s), 153.43 (s), 150.33 (s), 150.21 (s), 150.08 (s), 149.66 (s), 127.32 (d), 124.30 (d), 122.47 (d), 120.66 (d), 74.54 (d), 74.41 (d), 73.07 (d), 72.74 (d), 52.72 (q), 52.65 (q), 37.34 (q), 36.52 (q); MS m/z (relative intensity) 279 (M^+, 42), 137 (100); HRMS calcd for $C_{13}H_{13}NO_4S$ 279.0566, found 279.0562.

Dimethyl 4,7-Dihydro-8-isopropylbenzo[*b*]thiophen-4,7-imine-5,6-dicarboxylate (16c). The same procedure as that for **16b**: **1c** (165 mg, 1 mmol) and DMAD (185 mg, 1.3 mmol) reacted for 6 h to give **16c** as a yellow oil (292 mg, 95%). Spectral data indicated the presence of two invertomers: IR (neat) 3100–3080, 2960, 2870, 2740, 1740–1690, 1633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), at 50 °C δ 6.98 (d, 1 H, J = 4.5 Hz), 6.95 (d, 1 H, J = 4.5 Hz), 5.18 (d, 1 H, J = 1.0 Hz), 5.11 (d, 1 H, J = 1.2 Hz), 3.75 (s, 6 H), 2.65–2.55 (br s, 1 H), 1.03 (d, 3 H, J = 6.0 Hz), 1.02 (d, 3 H, J = 6.0 Hz); ^1H NMR (400 MHz, $CDCl_3$) at –50 °C showed two sets of peaks δ 7.01 (br s, 1.5 Hz), 6.92 (d, 0.5 Hz, J = 4.5 Hz), 5.30 (s, 0.5 H), 5.24 (s, 0.5 H), 5.20 (s, 0.5 Hz), 5.13 (s, 0.5 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 2.85–2.75 (m, 0.5 H), 2.47–2.37 (m, 0.5 Hz), 1.05 (d, 3 H, J = 6.1 Hz), 0.97 (t, 3 H, J = 6.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) at –50 °C δ 164.61 (s), 164.37 (s), 163.31 (s), 163.08 (s), 155.30 (s), 153.90 (s), 153.79 (s), 153.61 (s), 150.59 (s), 150.17 (s), 150.07 (s), 127.11 (d), 125.16 (d), 122.13 (d), 120.76 (d), 71.04 (d), 70.87 (d), 69.71 (d), 69.41 (d), 52.72 (q), 52.65 (q), 47.36 (d), 46.57 (d), 21.19 (q), 20.80 (q); MS m/z (relative intensity) 307 (M^+, 41), 165 (100); HRMS calcd for $C_{15}H_{17}NO_4S$: 307.0879, found 307.0882.

Dimethyl 4,7-Dihydro-8-*tert*-butylbenzo[*b*]thiophen-4,7-imine-5,6-dicarboxylate (16d). The same procedure as that for **16b**: **1d** (179 mg, 1 mmol) and DMAD (185 mg, 1.3 mmol) reacted for 6 h to give **16d** as a yellow oil (276 mg, 86%). Spectral data indicated the presence of two invertomers: IR (neat) 2980, 2960, 1730, 1710, 1635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) at 21 °C δ 6.93 (d, 1 H, J = 4.5 Hz), 6.90 (d, 1 H, J = 4.5 Hz), 5.28 (s, 1 H), 5.21 (s, 1 H), 3.75 (s, 6 H), 1.02 (s, 9 H); ^1H NMR spectram started to broaden at –50 °C, peak at 1.02 split into two broad peaks; MS m/z (relative intensity) 321 (M^+, 43), 179 (100); HRMS calcd for $C_{16}H_{19}NO_4S$ 321.1036, found 321.1039.

Dimethyl 4,7-Dihydro-8-benzylbenzo[*b*]thiophen-4,7-imine-5,6-dicarboxylate (16e). The same procedure as that for **16b**: **1e** (213 mg, 1 mmol) and DMAD (185 mg, 1.3 mmol) reacted for 10 h to give **16e** (286 mg, 84%) as a yellow oil. Spectral data indicated the presence of two invertomers: IR (neat) 3020, 2950, 2840, 1750–1690, 1633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) at 50 °C δ 7.32–7.24 (m, 5 H), 7.02–6.99 (m, 2 H), 4.97 (s, 1 H), 4.91 (s, 1 H), 3.75 (s, 6 H), 3.66 (br s, 2 H); ^1H NMR (400 MHz, $CDCl_3$) at –50 °C showed two sets of peaks δ 7.36–7.30 (m, 3 H), 7.25–7.21

(br t, 2 H), 7.10–7.08 (br s, 1.14 H), 7.00 (d, 0.43 H, J = 4.7 Hz), 6.92 (d, 0.43 H, J = 4.7 Hz), 5.12 (s, 0.43 H), 5.05 (s, 0.43 H), 4.98 (s, 0.57 H), 4.95 (s, 0.57 H), 3.85 (s, 0.86 H), 3.82 (s, 2.58 H), 3.74 (s, 3.42 H), 3.57 (s, 1.14 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) at −50 °C δ 164.87 (s), 164.66 (s), 163.40 (s), 163.18 (s), 155.33 (s), 154.15 (s), 153.99 (s), 153.69 (s), 150.53 (s), 150.23 (s), 136.84 (s), 136.44 (s), 129.49 (d), 129.22 (d), 128.49 (d), 127.49 (d), 127.39 (d), 125.26 (d), 122.55 (d), 120.97 (d), 72.47 (d), 72.33 (d), 70.90 (d), 69.77 (d), 54.35 (t), 53.34 (t), 52.76 (q), 52.56 (q); MS m/z (relative intensity) 355 (M^+, 87), 213 (100); HRMS calcd for $C_{19}H_{17}NO_4S$ 355.0879, found 355.0873.

Dimethyl 4,7-Dihydro-8-phenylbenzo[*b*]thiophen-4,7-imine-5,6-dicarboxylate (16f). The same procedure as that for **16b**: **1f** (199 mg, 1.0 mmol) and DMAD (185 mg, 1.3 mmol) reacted for 8 h to give **16f** (334 mg, 98%) as a yellow oil: IR (neat) 3020, 2960, 1740–1710, 1633 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) at 21 °C δ 7.22–7.18 (m, 2 H), 7.02 (d, 1 H, J = 4.6 Hz), 6.95 (d, 1 H, J = 4.6 Hz), 6.91–6.33 (m, 3 H), 5.83 (d, 1 H, J = 1.4 Hz), 5.77 (d, 1 H, J = 2.8 Hz), 3.77 (s, 6 H), the ^{1}H NMR spectrum does not change at different temperatures (50 °C to −50 °C); MS m/z (relative intensity) 341 (M^+, 100), 199 (50); HRMS calcd for $C_{18}H_{15}NO_4S$ 341.0723, found 341.0693.

Dimethyl 4,7-Dihydro-8-cyclohexylbenzo[*b*]thiophen-4,7-imine-5,6-dicarboxylate (16g). The same procedure as that for **16b**: **1g** (205 mg, 1 mmol) and DMAD (185 mg, 1.3 mmol) reacted for 8 h to give **16g** as a yellow oil (311 mg, 95%). Spectral data indicated the presence of two invertomers: IR (neat) 3080, 3020, 2940, 2850, 1750–1690, 1635 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) at 21 °C δ 6.99, 6.97 (AB q, 2 H, J = 4.4 Hz), 5.24 (s, 1 H), 5.18 (s, 1 H), 3.75 (s, 6 H), 2.35–2.20 (br s, 1 H), 1.80–1.65 (br s, 4 H), 1.60–1.50 (br s, 2 H), 1.30–1.15 (br m, 4 H); MS m/z (relative intensity) 347 (M^+, 64), 205 (100); HRMS calcd for $C_{18}H_{21}NO_4S$ 347.1192, found 347.1178.

Dimethyl 4,7-Dihydro-8-(carbomethoxymethyl)benzo[*b*]thiophen-4,7-imine-5,6-dicarboxylate (16h). The same procedure as that for **16b**: **1h** (195 mg, 1 mmol) and DMAD (185 mg, 1.3 mmol) reacted for 8 h to give **16h** (273 mg, 81%) as a yellow oil: IR (neat) 3080, 2995, 2970, 2840, 1750–1700, 1635 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) at 21 °C δ 7.02 (br s, 2 H), 5.25 (s, 1 H), 5.16 (s, 1 H), 3.75 (s, 6 H), 3.70 (s, 3 H), 3.35–3.25 (br s, 2 H); MS m/z (relative intensity) 337 (M^+, 82), 195 (100); HRMS calcd for $C_{15}H_{15}NO_6S$ 337.0620, found 337.0624.

Dimethyl 4,7-Dihydro-8-(*tert*-butoxycarbonyl)benzo[*b*]-thiopen-4,7-imine-5,6-dicarboxylate (16i). The same procedure as that for **16b**: **1i** (224 mg, 1 mmol) and DMAD (185 mg, 1.3 mmol) reacted for 8 h to give **16i** (300 mg, 82%) as a yellow oil: IR (neat) 3100, 2980, 2950, 1750–1700, 1630 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) at 29 °C δ 6.97 (br s, 2 H), 5.83 (br s, 1 H), 5.77 (br s, 1 H), 3.77 (s, 6 H), 1.37 (s, 9 H); MS m/z (relative intensity) 365 (M^+, 75), 223 (50), 167 (100), 123 (50); HRMS calcd for $C_{17}H_{19}NO_6S$ 365.0934, found 365.0925.

1:2 Cycloadducts 17 and 18 of *N*-Methylthieno[2,3-*c*]-pyrrole (1b) and Dimethyl Acetylenedicarboxylate. To a solution of compound **1b** (75% mg, 0.55 mmol) in benzene (10 mL) was added DMAD (184 mg, 1.3 mmol). The reaction mixture was stirred at room temperature for 27 h. Concentration and silica gel flash column chromatography (hexane–ethyl acetate, 2:1) gave a mixture of **17** and **18** (3:2, 224 mg, 97%), which were not separated: IR (KBr) 3150–3080, 3010–2990, 2960, 2880, 1760–1680, 1620 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 0.6 H), 7.64 (s, 0.4 H), 7.41 (d, 0.6 H, J = 5.12 Hz), 7.30 (d, 0.4 H, J = 4.97 Hz), 7.13–7.03 (m, 1 H), 5.19 (s, 0.4 H), 5.07 (s, 0.6 H), 3.86, 3.85, 3.74, 3.73, 3.71, 3.68, and 3.66 (7 s, 12 H), 2.75 (s, 1.2 H), 2.62 (s, 1.8 H); MS m/z (relative intensity) 421 (M^+, 10), 330 (100). Anal. Calcd for $C_{19}H_{19}NO_8S$: C, 54.15; H, 4.54; N, 3.23; S, 7.61. Found: C, 54.05; H, 4.53; N, 3.38; S, 7.59.

Dimethyl Benzo[*b*]thiophene-5,6-dicarboxylate (20).[10] To a solution of **16b** (90 mg, 0.5 mmol) in dichloromethane (20 mL) was added dropwise a solution of *m*-chloroperbenzoic acid (102 mg, 0.5 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at 20 °C for 30 min, and the mixture was washed with saturated sodium carbonate solution and dried (Na_2SO_4). Concentration and silica gel flash column chromatography (hexane–ethyl acetate, 3:1) gave **20** (103 mg, 82%) as a yellow oil: IR ($CHCl_3$) 3010, 2950, 1720, 1600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1 H), 8.15 (s, 1 H), 7.64 (d, 1 H, J = 5.2 Hz), 7.39 (d, 1 H, J = 5.2 Hz), 3.91 (s, 6 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.39 (s), 167.96 (s), 141.64 (s), 140.91 (s), 130.74 (d), 128.39 (s), 127.30 (s), 124.52 (d), 124.07 (d), 123.89 (d), 52.65 (q); MS m/z (relative intensity) 250 (M^+, 100), 219 (97).

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Registry No. **1a**, 250-63-5; **1b**, 119198-71-9; **1c**, 119198-72-0; **1d**, 119198-73-1; **1e**, 119198-74-2; **1f**, 119198-75-3; **1g**, 125302-60-5; **1h**, 125302-61-6; **1i**, 125302-62-7; **2**, 5834-16-2; **3**, 104085-29-2; **4**, 104085-30-5; **5**, 104085-31-6; **11**, 125302-63-8; **12**, 125302-64-9; **13**, 125302-65-0; **14a**, 125302-66-1; **14b**, 125302-67-2; **15a**, 125409-06-5; **15b**, 125409-07-6; **16b**, 125302-68-3; **16c**, 125302-69-4; **16d**, 125302-70-7; **16e**, 125302-71-8; **16f**, 125302-72-9; **16g**, 125329-33-1; **16h**, 125302-73-0; **16i**, 125302-74-1; **17**, 125302-75-2; **18**, 125302-76-3; **20**, 98449-83-3; DMAD, 762-42-5; diethyl malonate, 105-53-3; methyl glycinate hydrochloride, 5680-79-5; ethylenediamine, 107-15-3; 1,4-phenylenediamine, 106-50-3; *N*-phenylmaleimide, 941-69-5.

Supplementary Material Available: Spectroscopic and analytical data and reaction conditions for compounds **1c–g** (1 page). Ordering information is given on any current masthead page.