A General Synthetic Route to 2,2':5',2''-Terpyrrole, 2,5-Bis(2-pyrryl)thiophene, and Alkyl-Substituted Analogues

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A new four-step route to 2,2':5',2''-terpyrroles (**4**, **13**) and 2,5-bis(2-pyrryl)thiophenes (**6**, **14**) is described. The key step involves a Stetter reaction between an electron-deficient pyrrole aldehyde and divinyl sulfone. The resulting symmetrical 1,4-diketone is used as a common precursor for the synthesis of both tricyclic systems.

Introduction

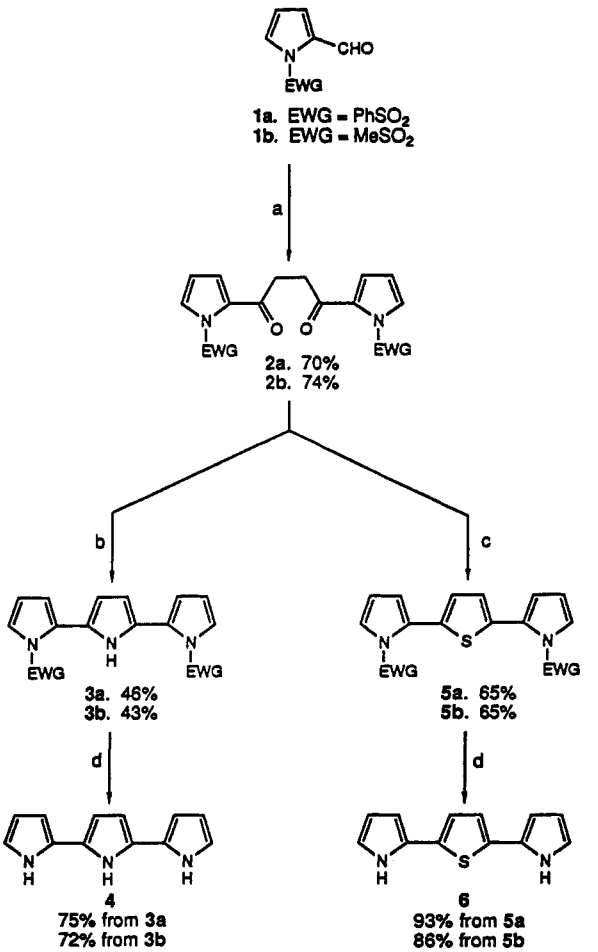
Present programs in our laboratory for the synthesis of porphyrin-like macrocycles and organic conductors require the use of α-oligo heteroaromatic compounds. Two specific compounds of interest to us are 2,2':5',2''-terpyrrole (**4**) and 2,5-bis(2-pyrryl)thiophene (**6**). The reported preparations of **4** are limited by low overall yields and lengthy reaction sequences, while the synthesis of **6** has not been reported.[1] Consequently, we sought to develop a general synthetic route to compounds **4** and **6** as well as their alkyl analogues **13** and **14**. In this paper, we describe an improved synthesis of **4** and the first syntheses of **6**, **13**, and **14**.[2]

Results and Discussion

Our strategy for the synthesis of 2,2':5',2''-terpyrrole (**4**) is outlined in Scheme I. The key step involves the formation of a 1,4-diketone from an appropriately substituted 2-formylpyrrole.[3] The preparation of symmetrical 1,4-diketones via the thiazolium salt catalyzed addition of heteroaromatic aldehydes to divinyl sulfone has been reported by Stetter for both 2-furyl and 2-thienyl aldehydes.[4] 2-Formylpyrrole, however, is unreactive to the Stetter conditions. This nonreactivity can be attributed to destabilization of the required β-hydroxy enamine intermediate by the electron-rich π-system of the pyrrole ring. The inability of 2-formylpyrrole to undergo the acyloin condensation provides evidence to support this reasoning.[5] The attachment of an electron-withdrawing group(s) (EWG) on the pyrrole ring has been shown to stabilize the reaction intermediate to the point where productive nucleophilic reactions can occur.[6] Jones has recently reported that EWG-substituted 2-formylpyrroles react with methyl vinyl ketone in thiazolium salt catalyzed Michael reactions.[7]

We synthesized a number of *N*-EWG-substituted 2-formylpyrroles and submitted them to the Stetter conditions. *N*-Acyl substituents (i.e., benzoyl, *tert*-butoxycarbonyl (BOC), and carbobenzyloxy (CBZ)) led to either deprotection of the pyrrole nitrogen or Cannizzaro reaction products, *N*-"alkyl"-based protecting groups (i.e., benzyl, pyridylethyl[8]) resulted in the recovery of starting material.

Scheme I[a]



[a] (a) Thiazolium salt catalyst, NaOAc, divinyl sulfone, EtOH, reflux; (b) NH_4OAc, Ac_2O, $C_2H_5CO_2H$, ultrasound followed by reflux; (c) Lawesson's reagent, toluene, reflux; (d) NaOH, MeOH, reflux.

Likewise, two *C*-EWG-substituted 2-formylpyrroles (i.e., 3-iodo and 5-cyanovinyl[9]) produced none of the desired 1,4-diketone product.

In contrast, 1-(phenylsulfonyl)-2-formylpyrrole (**1a**)[10] formed 1,4-diketone **2a** in 70% yield (see Scheme I). Compound **2a** precipitated out of the boiling ethanol solution as a fine tan powder. ^1H NMR spectroscopy revealed that the precipitate was >95% pure, and due to its insolubility in common organic solvents, **2a** was used without further purification.

Treatment of **2a** with ammonium acetate in refluxing propionic acid yielded the protected terpyrrole **3a** in 17%

(1) (a) Rapoport, H.; Castagnoli, N.; Holden, K. *J. Org. Chem.* **1964**, *29*, 883. (b) Chierici, L.; Cella, A. *Ann. Chim. (Rome)* **1960**, *43*, 141.
(2) A preliminary account of this work was presented at the 197th National Meeting of the American Chemical Society, Dallas, TX, April 9-14, 1989; paper ORGN 261.
(3) Reaction of the pyrrole Grignard reagent with diethyl succinate has been reported to provide the corresponding 1,4-diketone in low yield (22%). Chierici, L.; Serventi, G. *Gazz. Chim. Ital.* **1956**, *86*, 1278.
(4) Stetter, H.; Bender, H. *Chem. Ber.* **1981**, *114*, 1226.
(5) Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic Press: London, 1977; p 304.
(6) Bisagni, E.; Marquet, J.-P.; Andre-Louisfert, J. *Bull. Soc. Chim. Fr.* **1968**, 637.
(7) Hinz, W.; Jones, A.; Patel, U.; Karatza, M.-H. *Tetrahedron* **1986**, *42*, 3753.
(8) Katritzky, A. R.; Khan, G. R.; Marson, C. M. *J. Heterocycl. Chem.* **1987**, *24*, 641.
(9) Miller, R. M.; Olsson, K. *Acta. Chem. Scand. B* **1981**, *35*, 303. Paine, J. B.; Woodward, R. B.; Dolphin, D. *J. Org. Chem.* **1976**, *41*, 2826.
(10) Hinz, W.; Jones, R. A.; Anderson, T. *Synthesis* **1986**, 620.

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yield with 73% of **2a** recovered. We surmised that the poor yield for this reaction was due to the very low solubility of **2a** even in hot propionic acid and decided that ultrasound irradiation of the sample might create a more reactive medium.[11] Indeed, ultrasonic irradiation of the reaction mixture produced a fine dispersion which, upon subsequent refluxing, formed **3a** in 46% yield. The use of hexamethyldisilazane in place of ammonium acetate as the nitrogen source resulted in a comparable 44% yield of **3a**.[12]

Base hydrolysis of **3a** (NaOH/methanol) provided **4** in 75% yield after purification. The presence of an alkaline medium in the deprotection step is highly desirable due to the acid-sensitive nature of **4**. This synthetic route to **4** (four steps, 23% overall yield) compares favorably with Rapoport's previously reported synthesis (seven steps, 2.4% overall yield).[1a]

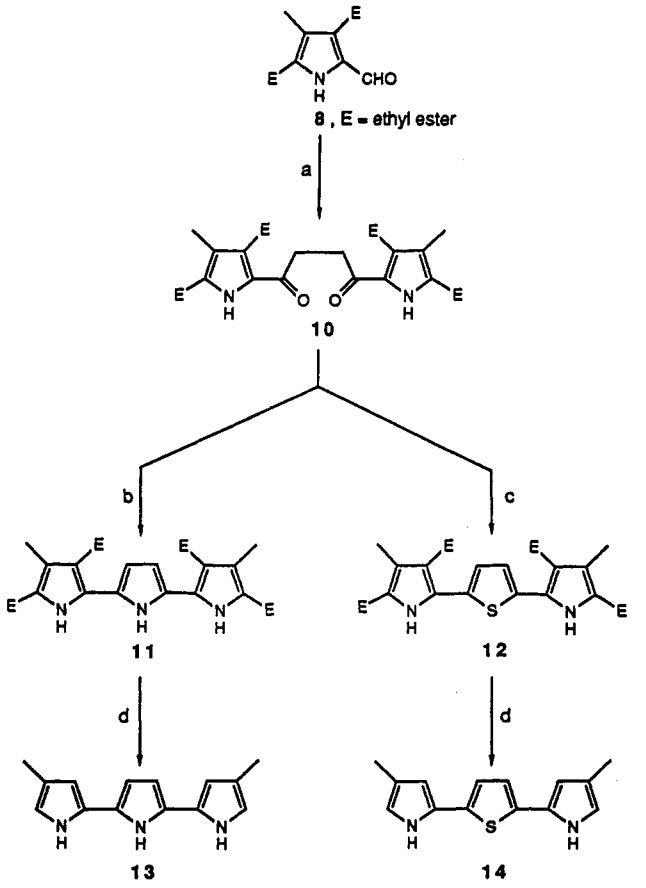
An additional advantage of our strategy is that it allows for the synthesis of novel mixed heteroaromatic systems such as **6** (see Scheme I).[13] Closure of the 1,4-diketone **2a** to a thiophene ring (**5a**) was accomplished in 65% yield with Lawesson's reagent.[13a,14] Ultrasound irradiation was not required in this step. Base hydrolysis of the phenylsulfonyl groups provided **6** in 93% yield.

Although the use of the *N*-(phenylsulfonyl) group to temporarily activate 2-formylpyrrole provided a facile route to tricycles **4** and **6**, the high molecular weight of the protecting group posed a practical inconvenience. Thus, we investigated the use of the methylsulfonyl group as a lower molecular weight activating substituent. Scheme I shows that comparable yields of both **4** and **6** were obtained using **1b** in place of **1a** in the reaction sequence.

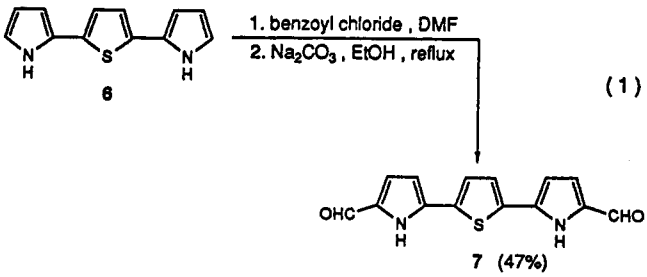
The only deviation occurred in the synthesis of **1b**. While **1a** was formed in high yield (96%) by the addition of benzenesulfonyl chloride to 2-formylpyrrole according to the phase-transfer conditions of Jones,[10] the same conditions provided only a modest amount of **1b** (42%). An optimized yield of **1b** (61%) was obtained by the slow addition of methanesulfonyl chloride to the preformed pyrrole anion (NaH/ether). The difficulty in formation of **1b** relative to **1a** may be due to the presence of acidic protons on the methyl group of methanesulfonyl chloride. For example, the production of sulfene ($CH_2{=}SO_2$) by monodeprotonation of either methanesulfonyl chloride or **1b** may result in competitive dimerization and oligomerization reactions.[15]

We were interested next in the synthesis of substituted analogues of **4** and **6**. As expected, formylation of **6** demonstrated that the 5- and 5″-positions on the two pyrrole rings are the most reactive sites toward electrophilic aromatic substitution. Clezy's modification of the Vilsmeier reaction for acid-sensitive compounds provided 2,5-bis(5-formyl-2-pyrryl)thiophene (**7**) in 47% yield (see eq 1).[16] Compound **7** exhibited extremely low solubility in common organic solvents. This property is in accord with the physical characteristics of other linear, heteroaromatic dialdehydes.[17]

Scheme II[a]



[a] (a) Thiazolium salt catalyst, Et_3N, divinyl sulfone, dioxane, 80 °C, 60%; (b) NH_4OAc, HOAc, Ac_2O, reflux, 75%; (c) Lawesson's reagent, toluene, reflux, 76%; (d) (i) NaOH, EtOH, reflux, (ii) sublimation (22% yield of **13**, 52% yield of **14**).



(1)

Alkyl-substituted analogues were synthesized by the use of 2-formyl-3,5-bis(ethoxycarbonyl)-4-methylpyrrole (**8**)[18] as the activated aldehyde in the general four-step procedure (see Scheme II). In this case, the electron density of the pyrrole ring was reduced by the addition of two ethyl ester substituents on the C-3 and C-5 positions of the aldehyde. Submission of **8** to the Stetter reaction provided the 1,4-diketone **10** in 60% yield.[19] Closure of **10** to the corresponding pyrrole (**11**, 75%) and thiophene (**12**, 76%)

(11) Suslick, K. S. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1986; Vol. 4, pp 1–57.
(12) Rigo, B.; Valligny, D.; Taisne, S. *Synth. Commun.* **1988**, *18*, 167.
(13) For examples of related mixed heteroaromatic systems see: (a) Wynberg, H.; Metselaar, J. *Synth. Commun.* **1984**, *14*, 1. (b) Ferraris, J. P.; Skiles, G. D. *Polymer* **1987**, *28*, 179. (c) Naitoh, S. *Synth. Met.* **1987**, *18*, 237.
(14) (a) Pederson, B. S.; Scheibye, S.; Nilsson, N. H.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 223. (b) Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061. (c) Shridhar, D. R.; Jogibhukta, M.; Rao, P. S.; Handa, V. K. *Synthesis* **1982**, 1061.
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(16) Chong, R.; Clezy, P. S.; Liepa, A. J.; Nichol, A. W. *Aust. J. Chem.* **1969**, *22*, 229.
(17) Luo, T. H. Ph.D. Thesis, Michigan State University, 1987. Leung, W.-Y., Ph.D. Thesis, Michigan State University, 1988.
(18) Corwin, A. H.; Bailey, W. A.; Viohl, P. *J. Am. Chem. Soc.* **1942**, *64*, 1267.
(19) Submission of an aldehyde with only one ethyl ester substituent (2-formyl-5-(ethoxycarbonyl)-3,4-dimethylpyrrole (**9**)) to the Stetter conditions resulted in a poor yield of the corresponding 1,4-diketone (33%). The dramatic difference in product yield for aldehydes **8** and **9** (2:1) reveals the effect of electron-withdrawing group(s) strength on the efficiency of the Stetter reaction.

products proceeded readily using the standard conditions. Since **10** was soluble in hot HOAc, ultrasonic treatment was not required for the preparation of **11**. Saponification and subsequent decarboxylation of tetraester **11** provided the 4,4″-dimethyl-substituted compound **13** in 22% yield. Identical treatment of **12** produced **14** in 52% yield.

In conclusion, we have described a general and efficient route to 2,2′:5′,2″-terpyrrole (**4**) and 2,5-bis(2-pyrryl)-thiophene (**6**), a new linear heteroaromatic tricycle. The utilization of a 1,4-diketone moiety in the synthetic strategy allows for both systems to be obtained from a single precursor.

Investigations into the conductive polymer aspects of this project are in progress, and our results in this area will be reported at a later date.

Experimental Section

General. Toluene and diethyl ether were dried by distillation under argon from sodium benzophenone ketyl. Acetic anhydride, triethylamine (TEA), and methanesulfonyl chloride were dried by distillation under argon from calcium hydride. Ethanol was dried by distillation under argon from magnesium. Acetic acid (HOAc) was dried by distillation under argon from triacetyl borate.[20] Anhydrous *N,N*-dimethylformamide (DMF) and 1,4-dioxane were purchased from Aldrich Chemical Co., Milwaukee, WI, and used as received. Ammonium acetate (NH_4OAc) and sodium acetate (NaOAc) were dried in a vacuum oven at 50 °C and 100 °C, respectively. All reactions were performed under an argon atmosphere unless otherwise mentioned.

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ultrasonic processing was performed with a Vibra Cell VC500. Proton nuclear magnetic resonance (^1H NMR) spectra were obtained on a Bruker WM-250 (250 MHz), a Varian VXR (300 MHz), or a Varian Gemini (300 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) using the residual solvent proton resonance as the internal reference (acetone, δ 2.04; acetonitrile, 1.93; chloroform, 7.24; dichloromethane, 5.32; DMSO, 2.49; methanol, 3.30; tetrahydrofuran, 1.73). ^1H NMR data are tabulated as follows: chemical shift multiplicity (s, singlet; br s, broad singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet), coupling constant (hertz), number of hydrogens. ^{13}C nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker WM-250 (62.9 MHz), a Varian VXR (75.4 MHz), or a Varian Gemini (75.4 MHz). Chemical shift values are reported in parts per million using the solvent peak as the internal reference (acetone, δ 29.8; chloroform, 77.0; DMSO, 39.5; methanol, 49.0; tetrahydrofuran, 67.4). Infrared (IR) spectra were recorded on a Nicolet IR/42 spectrometer. Ultraviolet (UV) spectra were obtained on a Hitachi U-2000 spectrometer. Electron impact mass spectra (EI-MS) were recorded on a Finnigan 4000 with an INCOS 4021 data system. High-resolution mass spectra (HRMS) were determined on a JEOL HX110 spectrometer at the Michigan State University Regional Mass Spectroscopy Facility (Biomedical Research Technology Program, NIH funded DRR-0480), Department of Biochemistry, East Lansing, MI.

Flash column chromatography was performed according to the procedure of Still et al.[21] Chromatography parameters are reported as follows: grams of solid phase, column outer diameter (o.d.), eluent, R_f.

1-(Methylsulfonyl)-2-formylpyrrole (1b). A suspension of NaH (1.0 g, 25 mmol, 60% in oil washed with 3 × 50-mL portions of dry ether) in ether (50 mL) was slowly charged with 2-formylpyrrole (20 mL of 1.37 M ether solution, 27 mmol), and the flask was heated to a gentle reflux for 2.5 h. Methanesulfonyl chloride (8 mL of 3.72 M ether solution, 30 mmol) was added dropwise at 0 °C, and the resulting tan suspension was stirred for 5 h at 0 °C followed by 35 h at room temperature. The mixture was filtered and washed with CH_2Cl_2, and the filtrate was concentrated in vacuo to provide a brown oil. The crude product was purified by flash column chromatography (200 g of 230–400-mesh silica gel, 50 mm o.d. column, CH_2Cl_2–EtOAc (99:1), R_f 0.45) to yield 2.65 g (61%) of **1b** as a pale yellow oil which solidifies upon standing: mp 43–44 °C; ^1H NMR (acetone-d_6) δ 9.76 (d, J = 0.8 Hz, 1 H), 7.61 (ddd, J = 3.1, 1.8, 0.8 Hz, 1 H), 7.35 (dd, J = 3.9, 1.8 Hz, 1 H), 6.48 (dd, J = 3.9, 3.1 Hz, 1 H), 3.73 (s, 3 H); ^{13}C NMR (acetone-d_6) δ 179.2, 134.2, 130.8, 128.4, 112.2, 43.0; IR (Nujol) 3140, 3128, 1674, 1445, 1408, 1362, 1339, 1327, 1236, 1177, 1142, 1061, 1019, 970, 779, 772 cm^{-1}; EI-MS (70 eV) m/z (relative intensity) 173 (M^+, 10.0), 94 (73.4), 79 (22.6), 66 (20.3).

1,4-Bis(1-(phenylsulfonyl)-2-pyrryl)-1,4-butanedione (2a). A mixture of **1a** (21.0 g, 89.4 mmole) in absolute ethanol (120 mL) was charged with 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (3.7 g, 13.6 mmol) and anhydrous NaOAc (2.3 g, 23.0 mmol). The mixture was heated to a gentle reflux, and divinyl sulfone (4.5 ml, 43.8 mmol) was added dropwise. The solution was refluxed for an additional 12 h. A light tan precipitate was filtered from the orange solution and washed with cold water, ethanol, and ether. The precipitate was air-dried to yield 15.6 (70%) of **2a** as a fine powder (>95% pure by ^1H NMR spectroscopy). Flash column chromatography (230–400-mesh silica gel, CH_2Cl_2, R_f 0.31) provided an analytical sample of **2a** as a white solid: mp 206–207 °C; ^1H NMR ($CDCl_3$) δ 7.95 (d, J = 7.7 Hz, 4 H), 7.80 (m, 2 H), 7.57–7.45 (m, 6 H), 7.12 (dd, J = 3.8, 1.6 Hz, 2 H), 6.35 (t, J = 3.4 Hz, 2 H), 3.03 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 186.6, 138.9, 133.6, 132.8, 130.2, 128.7, 128.0, 123.8, 110.5, 33.0; IR (Nujol) 1674, 1358, 1290, 1175, 1144, 1111, 1063, 1046, 964, 773, 748, 680 cm^{-1}; EI-MS (70 eV) m/z (relative intensity) 496 (M^+, 2.2), 339 (6.1), 262 (21.6), 234 (68.9), 141 (32.1), 94 (30.4), 77 (base); HRMS (FAB) calcd for $C_{24}H_{20}N_2O_6S_2$ (M + H) 497.0841, found 497.0835.

1,4-Bis(1-(methylsulfonyl)-2-pyrryl)-1,4-butanedione (2b). The same general procedure as for the formation of **2a** was used. Compound **1b** (2.0 g, 12 mmol), divinyl sulfone (0.57 mL, 5.6 mmol), NaOAc (0.3 g, 3.6 mmol), 3-benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium chloride (0.48 g, 1.8 mmol), and absolute ethanol were combined to yield 1.56 g (74%) of **2b** as a light tan solid (>95% pure by ^1H NMR spectroscopy). Flash column chromatography (230–400-mesh silica gel, CH_2Cl_2, R_f 0.27) provided an analytical sample of **2b** as a white solid: mp 195–197 °C; ^1H NMR (CD_2Cl_2) δ 7.57 (dd, J = 3.3, 1.7, Hz, 2 H), 7.30 (dd, J = 3.6, 1.7 Hz, 2 H), 6.35 (dd, J = 3.6, 3.3 Hz, 2 H), 3.65 (s, 6 H), 3.27 (s, 4 H); ^{13}C NMR (DMSO-d_6) δ 188.0, 132.2, 129.8, 124.8, 110.3, 42.5, 32.6; IR (Nujol) 1659, 1366, 1288, 1109, 1040, 947 cm^{-1}; EI-MS (70 eV) m/z (relative intensity) 372 (M^+, 1.7), 200 (16.7), 172 (55.9), 94 (base), 79 (28.9); HRMS (FAB) calcd for $C_{14}H_{16}N_2O_6S_2$ (M + H) 373.0528, found 373.0529.

2,5-Bis(1-(phenylsulfonyl)-2-pyrryl)pyrrole (3a). A suspension of **2a** (0.401 g, 0.81 mmol) in dry propionic acid (6 mL) was charged with anhydrous NH_4OAc (1.71 g, 22.2 mmol) and acetic anhydride (1.20 mL, 12.7 mmol). The reaction mixture was cooled in a water bath and sonicated with a direct immersion ultrasonic horn until a fine dispersion was obtained.[11] The water bath temperature never exceeded 30 °C. The tan dispersion was quickly decanted into a round-bottom flask fitted with a condenser and heated to a gentle reflux for 10 h. After cooling to room temperature, a majority of the propionic acid and acetic anhydride was removed by vacuum distillation. Water (20 mL) was added to the residue, and this solution was neutralized with 2 N NaOH. The aqueous solution was extracted with CH_2Cl_2, and the combined organic fractions were washed with 10% sodium bicarbonate (2×) and brine (1×), dried over Na_2SO_4, and concentrated in vacuo. Flash column chromatography (15 g of 230–400-mesh silica gel, 20 mm o.d. column, CH_2Cl_2–hexane (75:25), R_f 0.44) provided 0.178 g (46%) of **3a** as a pale yellow solid: mp 151–152 °C; ^1H NMR (acetone-d_6) δ 9.95 (br s, 1 H), 7.67–7.44 (m, 12 H), 6.35 (m, 4 H), 6.21 (d, J = 2.6 Hz, 2 H; ^{13}C NMR (acetone-d_6) δ 139.2, 134.9, 130.0, 128.7, 127.9, 124.6, 122.9, 116.6, 113.0, 112.4; EI-MS (25 eV) m/z (relative intensity) 477 (M^+, 10.7), 336 (68.7), 195 (base); UV (methanol) 288 (log ϵ 4.06), 275 (4.07), 224 nm (4.33); HRMS (EI) calcd for $C_{24}H_{19}N_3O_4S_2$ 477.0817, found 477.0797.

2,5-Bis(1-(methylsulfonyl)-2-pyrryl)pyrrole (3b). The same procedure as for the formation of **3a** was used. Compound **2b** (0.507 g, 1.4 mmol), NH_4OAc (2.82 g, 36 mmol), acetic anhydride (1.9 mL, 20 mmol), and propionic acid (11 mL) were combined. Flash column chromatography of the crude product (30 g of

(20) Eichelberger, W. C.; LaMer, K. *J. Am. Chem. Soc.* **1933**, *55*, 3633.
(21) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

230–400-mesh silica gel, 30 mm o.d. column, CH_2Cl_2, R_f 0.42) yielded 0.207 g (43%) of **3b** as a white solid: mp 107–108 °C; ^1H NMR (acetone-d_6) δ 10.19 (br s, 1 H), 7.26 (dd, J = 3.4, 1.8 Hz, 2 H), 6.50 (m, 4 H), 6.36 (t, J = 3.4 Hz, 2 H), 3.18 (s, 6 H); ^{13}C NMR (acetone-d_6) δ 127.5, 123.8, 123.3, 116.2, 112.5, 111.8 42.1; EI-MS (25 eV) m/z (relative intensity) 353 (M^+, base), 274 (47.0), 196 (98.2); UV (methanol) 290 nm (log ε 4.13); HRMS (FAB) calcd for $C_{14}H_{15}N_3O_4S_2$ (M + H) 354.0582, found 354.0590.

2,2':5',2''-Terpyrrole (4). A deaerated solution of NaOH (5 N, 2 mL) in methanol (7 mL) was charged with **3a** (0.200 g, 0.42 mmol) and heated to a gentle reflux for 70 min. The reaction was cooled to room temperature and extracted from NH_4Cl (sat.) with CH_2Cl_2. The combined organic fractions were washed with water (2×), dried over Na_2SO_4, and concentrated in vacuo. The dark gray residue was immediately purified by flash column chromatography (6 g of 230–400-mesh silica gel, 15 mm o.d. column, argon pressure, deaerated CH_2Cl_2–EtOAc (98:2), R_f 0.36) to provide 62 mg (75%) of **4** as a light gray solid. Sublimation (180 °C, 0.1 mmHg) provided an analytical sample of **4** as a white solid, mp 241–242 °C (lit.[1a] mp 242 °C). Compound **4** was stored at 15 °C under an argon atmosphere. The ^1H NMR and UV spectra of **4** are consistent with literature values:[1a] ^1H NMR (methanol-d_4) δ 6.66 (dd, J = 2.6, 1.5 Hz, 2 H), 6.27 (dd, J = 3.4, 1.5 Hz, 2 H), 6.18 (s, 2 H), 6.08 (dd, J = 3.4, 2.6 Hz, 2 H); ^{13}C NMR (methanol-d_4) δ 127.5, 127.2, 117.9, 109.3, 104.5, 103.5; EI-MS (25 eV) m/z (relative intensity) 197 (M^+, base), 196 (46.3), 169 (21.5); UV (methanol) 345 sh (log ε 4.07), 326 (4.37), 319 nm (4.38); HRMS (EI) calcd for $C_{12}H_{11}N_3$ 197.0953, found 197.1010.

2,5-Bis(1-(phenylsulfonyl)-2-pyrryl)thiophene (5a). A mixture of **2a** (8.0 g, 16 mmol) in dry toluene (225 mL) was charged with Lawesson's reagent[14] (4.6 g, 11 mmol) and heated to a gentle reflux for 6 h. The green solution was cooled to room temperature and concentrated to half its original volume in vacuo. Methanol was slowly added to the toluene solution until a precipitate appeared. Filtration yielded 5.5 g of a light tan solid. Flash column chromatography of the crude product (300 g of 230–400-mesh silica gel, 50 mm o.d. column, CH_2Cl_2–hexane (60:40), R_f 0.48) provided 5.2 g (65%) of **5a** as a white solid: mp 151–152 °C; ^1H NMR ($CDCl_3$) δ 7.57–7.38 (m, 12 H), 6.95 (s, 2 H), 6.27 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 138.4, 133.8, 132.5, 129.9, 129.1, 127.3, 126.8, 124.8, 117.7, 111.9; EI-MS (70 eV) m/z (relative intensity) 494 (M^+, 5.1), 353 (30.5), 212 (base), 141 (11.4), 77 (82.2); UV (methanol) 298 (log ε 4.0), 275 (3.94), 268 (3.92), 217 nm (4.31); HRMS (EI) calcd for $C_{24}H_{18}N_2O_4S_3$ 494.0429, found 494.0396.

2,5-Bis(1-(methylsulfonyl)-2-pyrryl)thiophene (5b). The same general procedure as for the formation of **5a** was used. Compound **2b** (0.201 g, 0.54 mmol), Lawesson's reagent (0.153 g, 0.38 mmol), and toluene (10 mL) were heated to a gentle reflux for 4 h. Flash column chromatography of the crude product (20 g of 230–400-mesh silica gel, 20 mm o.d. column, CH_2Cl_2, R_f 0.46) yielded 0.130 g (65%) of **5b** as a white solid: mp 155–157 °C; ^1H NMR (acetone-d_6) δ 7.35 (dd, J = 3.4, 1.8 Hz, 2 H), 7.31 (s, 2 H), 6.54 (dd, J = 3.5, 1.8 Hz, 2 H), 6.39 (t, J = 3.4 Hz, 2 H), 3.23 (s, 6 H); ^{13}C NMR (acetone-d_6) δ 133.8, 130.6, 126.8, 125.1, 118.2, 112.0, 42.6; EI-MS (70 eV) m/z (relative intensity) 372 (M + 2, 1.4), 371 (M + 1, 197), 370 (M^+, 12.8), 291 (35.3), 212 (base), 79 (43.6); UV (methanol) 303 nm (log ε 4.10); HRMS (FAB) calcd for $C_{14}H_{14}N_2O_4S_3$ (M + H) 371.0194, found 371.0196.

2,5-Bis(2-pyrryl)thiophene (6). The same general procedure as for the formation of **4** was used. Compound **5a** (0.203 g, 0.4 mmole), NaOH (2 mL, 5 N), and methanol (5 mL) were refluxed for 1.5 h to achieve the desired hydrolytic deprotection. Column chromatography with neutral alumina (9 g of 80–200-mesh silica gel, 15 mm o.d. column, deaerated CH_2Cl_2–EtOAc (97:3), R_f 0.36) provided 82 mg (93%) of **6** as a pale green solid: mp 194–196 °C dec; ^1H NMR (acetone-d_6) δ 10.40 (br s, 2 H), 7.05 (s, 2 H), 6.80 (m, 2 H), 6.30 (m, 2 H), 6.12 (m, 2 H); ^{13}C NMR (acetone-d_6) δ 134.3, 127.3, 121.6, 119.6, 110.0, 106.8; EI-MS (70 eV) m/z (relative intensity) 216 (M + 2, 5.0), 214 (M^+, base), 186 (19.3), 107 (9.6); UV (methanol) 377 sh (log ε 4.11), 353 (4.40), 226 nm (4.01); HRMS (EI) calcd for $C_{12}H_{10}N_2S$ 214.0565, found 214.0572.

2,5-Bis(5-formyl-2-pyrryl)thiophene (7). A magnetically stirred solution of **6** (0.100 g, 0.47 mmol) in anhydrous DMF (3 mL) was cooled to 0 °C and slowly charged with benzoyl chloride (3.5 mL of 1.2 M DMF solution, 4.2 mmol). The solution was stirred at 0 °C for 1 h and then warmed to 80 °C for 6 h. After cooling to room temperature, toluene (5 mL) was added to the reaction. The resulting precipitate was collected and transferred to a flask containing Na_2CO_3 (0.15 g) in aqueous ethanol (70%, 10 mL). The green solution was heated at reflux temperature for 0.5 h followed by stirring at room temperature for 7 h. Removal of the ethanol in vacuo provided an aqueous residue which was extracted with CH_2Cl_2. The combined organic fractions were washed with water (2×), dried over Na_2SO_4, and concentrated to yield a yellow solid (14 mg). In addition, filtration of an emulsion at the water/CH_2Cl_2 interface yielded a dark green solid (57 mg). The crude samples were combined. Recrystallization from acetonitrile provided 59 mg (47%) of **7** as dark green needles: mp 275–276 °C; ^1H NMR (DMSO-d_6) δ 12.58 (br s, 2 H), 9.49 (s, 2 H), 7.68 (s, 2 H), 7.07 (d, J = 4.0 Hz, 2 H), 6.57 (d, J = 4.0 Hz, 2 H); ^{13}C NMR (DMSO-d_6) δ 178.7, 133.6, 133.4, 133.3, 125.7, 122.1, 109.2; IR (Nujol) 3262, 1637, 1273, 1049, 1041, 829, 781, 771 cm^{-1}; EI-MS (25 eV) m/z (relative intensity) 272 (M + 2, 5.3), 271 (M + 1, 14.7), 270 (M^+, base), 241 (12.7), 214 (20.7), 213 (22.2), 186 (11.2); UV (acetonitrile) 409 sh (log ε 4.42), 392 (4.55), 375 sh (4.49), 245 (4.05), 222 nm (4.10); HRMS (FAB) calcd for $C_{14}H_{10}N_2O_2S$ (M + H) 271.0541, found 271.0523.

1,4-Bis(3,5-bis(ethoxycarbonyl)-4-methyl-2-pyrryl)-1,4-butanedione (10). A solution of **8** (8.5 g, 33 mmol) in anhydrous 1,4-dioxane (70 mL) was charged with 3,4-dimethyl-5-(2-hydroxyethyl)thiazolium iodide (1.4 g, 5 mmol) and triethylamine (1.4 mL, 10 mmol). The mixture was heated to 85 °C, and divinyl sulfone (1,6 mL, 16 mmol) was added dropwise. The solution was stirred at 85–90 °C for an additional 20 h. The reaction was cooled and filtered, and the filtrate was concentrated in vacuo. The bright orange residue was extracted from water with CH_2Cl_2. The combined organic fractions were washed with water (2×), dried over $MgSO_4$, and concentrated. The crude product was dissolved in a minimum amount of CH_2Cl_2, and dropwise addition of ether resulted in the precipitation of 5.1 g (60%) of **10** as a light tan powder (>95% pure by ^1H NMR spectroscopy). Flash column chromatography (230–400-mesh silica gel, hexane–EtOAc (70:30), R_f 0.30) provided an analytical sample of **10** as a white solid: mp 153–154 °C; ^1H NMR ($CDCl_3$) δ 9.97 (br s, 2 H), 4.41 (q, J = 7.1 Hz, 4 H), 4.35 (q, J = 7.1 Hz, 4 H), 3.40 (s, 4 H), 2.48 (s, 6 H), 1.39 (t, J = 7.1 Hz, 6 H), 1.34 (t, J = 7.1 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 190.1, 163.9, 159.4, 130.8, 128.5, 121.2, 118.9, 60.2, 60.0, 34.1, 13.3, 13.2, 10.4; IR (Nujol) 3277, 1701, 1665, 1556, 1337, 1281, 1250, 1184, 1130, 1024, 870, 792, 775 cm^{-1}; EI-MS (70 eV) m/z (relative intensity) 532 (M^+, 1.2), 440 (10.7), 261 (13.8), 252 (68.6), 234 (base), 206 (68.8), 188 (56.6), 178 (65.8); HRMS (FAB) calcd for $C_{26}H_{32}N_2O_{10}$ (M + H) 533.2135, found 533.2129.

2,5-Bis(3,5-bis(ethoxycarbonyl)-4-methyl-2-pyrryl)pyrrole (11). The same general procedure as for the formation of **3a** was used. A major change in the experimental procedure was the elimination of the ultrasound treatment. Compound **10** is soluble in hot HOAc. Compound **10** (4.0 g, 7.5 mmol), NH_4OAc (14.4 g, 187 mmol), acetic anhydride (5.9 mL, 62 mmol), and HOAc (100 mL) were heated at reflux for 12 h. Flash column chromatography of the crude product (200 g of 230–400-mesh silica gel, 50 mm o.d. column, hexane–EtOAc (70:30), R_f 0.31) yielded 2.9 g (75%) of **11** as a yellow solid: mp 163–164 °C; ^1H NMR (acetone-d_6) δ 12.57 (br s, 1 H), 10.80 (br s, 2 H), 6.88 (d, J = 2.3 Hz, 2 H), 4.33 (q, J = 7.1 Hz, 4 H), 4.29 (q, J = 7.1 Hz, 4 H), 2.60 (s, 6 H), 1.32 (t, J = 7.2 Hz, 12 H); ^{13}C NMR (acetone-d_6) δ 166.7, 161.6, 133.5, 131.4, 124.9, 120.6, 112.9, 111.4, 61.0, 60.7, 14.7, 14.6, 12.6; IR (Nujol) 3320, 3243, 1695, 1657, 1576, 1253 cm^{-1}; EI-MS (70 eV) m/z (relative intensity) 513 (M^+, 52.7), 467 (55.5), 421 (base), 330 (13.7), 274 (28.5), 165 (26.0); UV (methanol) 367 (log ε 4.46), 303.5 (4.19), 220 (4.53); HRMS (EI) calcd for $C_{26}H_{31}N_3O_8$ 513.2111, found 513.2057.

2,5-Bis(3,5-bis(ethoxycarbonyl)-4-methyl-2-pyrryl)-thiophene (12). The same general procedure as for the formation of **5a** was used. Compound **10** (4.2 g, 7.9 mmol), Lawesson's reagent (2.1 g, 5.2 mmol), and toluene (80 mL) were heated to a gentle reflux for 4 h. Flash column chromatography of the crude product (300 g of 230–400-mesh silica gel, 50 mm o.d. column, CH_2Cl_2–EtOAc (95:5), R_f 0.36) yielded 3.2 g (76%) of **12** as a pale yellow solid: mp 146–147 °C; ^1H NMR ($CDCl_3$) δ 9.11 (br s, 2 H), 7.42 (s, 2 H), 4.32 (q, J = 7.1 Hz, 4 H), 4.27 (q, J = 7.1 Hz, 4 H), 2.59 (s, 6 H), 1.34 (t, J = 7.1 Hz, 6 H), 1.30 (t, J = 7.1 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 164.7, 161.1, 133.8, 131.7, 130.9, 128.3,

120.2, 114.9, 60.7 60.2, 14.4, 14.3, 12.0; IR (Nujol) 3436, 3326, 1709, 1682, 1269, 1250, 1128, 1101, 1065, 1024, 783 cm^{-1}; EI-MS (70 eV) m/z (relative intensity) 530 (M^+, 6.2), 484 (10.1), 438 (12.3); UV (methanol) 340 (log ϵ 4.28), 275 nm (4.21); HRMS (EI) calcd for $C_{26}H_{30}N_2O_8S$ 530.1722, found 530.1694.

2,5-Bis(4-methyl-2-pyrryl)pyrrole (13). A deaerated solution of NaOH (3 N, 15 mL) in ethanol (25 mL) was charged with **11** (0.600 g, 1.2 mmol) and heated to a gentle reflux for 12 h. The reaction was cooled to room temperature, and ethanol was removed in vacuo. Water and CH_2Cl_2 were added. The aqueous layer was separated, cooled in an ice bath, and slowly acidified to pH 4 with HOAc. The resulting mixture was filtered to yield 540 mg of a black percipitate (crude tetraacid). The crude product was dried on a mechanical vacuum pump (0.05 mmHg) overnight. Sublimation of the dry solid (200 °C, 0.1 mmHg) provided 57 mg (22%) of **13** as a white powder: mp 229-231 °C; ^1H NMR (acetonitrile-d_3) δ 9.15 (br s, 1 H), 8.91 (br s, 2 H), 6.47 (s, 2 H), 6.14 (d, J = 2.6 Hz, 2 H), 6.10 (s, 2 H), 2.06 (s, 6 H); ^{13}C NMR (methanol-d_4) δ 127.3, 127.0, 119.7, 115.6, 104.9, 104.2, 11.7; EI-MS (25 eV) m/z (relative intensity) 225 (M^+, base), 210 (14.8), 111 (13.3), 97 (19.0); UV (methanol) 325 nm (log ϵ 4.46); HRMS (EI) calcd for $C_{14}H_{15}N_3$ 225.1266, found 225.1281.

2,5-Bis(4-methyl-2-pyrryl)thiophene (14). The same general procedure as for the formation of **13** was used. Saponification of **12** (0.350 g, 0.56 mmol) yielded 0.285 g of crude tetraacid as a dark green solid. Sublimation (200 °C, 0.1 mmHg) provided 83 mg (52%) of **14** as a pale yellow powder: mp 237-238 °C; ^1H NMR (THF-d_8) δ 9.96 (br s, 2 H), 6.85 (s, 2 H), 6.47 (s, 2 H), 6.10 (s, 2 H), 2.06 (s, 6 H); ^{13}C NMR (THF-d_8) δ 134.6, 127.5, 120.7, 120.1, 117.2, 108.1, 12.0; EI-MS (25 eV) m/z (relative intensity) 244 (M + 2, 5.7), 243 (M + 1, 17.3), 242 (M^+, base), 149 (10.6); UV (methanol) 362 nm (log ϵ 4.41); HRMS (FAB) calcd for $C_{14}H_{14}N_2S$ (M + H) 243.0956, found 243.0939.

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Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra for all of the compounds reported in the Experimental Section (30 pages). Ordering information is given on any current masthead page.

An Unusual Fischer Indole Synthesis with 4-Keto Acids: An Indole Incorporating the Terminal Hydrazine Nitrogen

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During preparation of a pharmaceutically active, N-benzylated indole derivative from 4-keto acid and N_1-benzylated phenylhydrazine precursors, the N-unsubstituted indole analogue arose as a significant byproduct. The proportion of debenzylated indole was greater with α-alkylated rather than straight-chain keto acids and the byproduct was fully suppressed when a keto ester was substituted for the keto acid. The benzylic group was shown to have eliminated as the amine and ^{15}N label incorporation demonstrated terminal phenylhydrazine nitrogen incorporation in the indole byproduct only, an exception to the usual course of the Fischer indolization reaction. A ring-chain equilibration in the ketimino acid intermediate is proposed to account for the competing pathway.

Introduction

The mechanism of the Fischer indole synthesis has been the subject of investigations by numerous workers.[2] In particular, isotopic labeling studies clearly established the N_1 (aryl) nitrogen atom of phenylhydrazine precursors as that incorporated into the indole nucleus.[3] But when re-aromatization in the normal indolization route was purposely blocked, e.g., in 2,6-dialkylphenylhydrazines, non-indole or rearranged indole type products were isolated, usually in only poor to fair yield, with the terminal nitrogen incorporated.[4] We now report indolizations using simple phenylhydrazines and keto acids, in which significant indole byproducts arise bearing the terminal phenylhydrazine nitrogen while principal indole products concomitantly incorporate the usual N_1. Nitrogen-15 label studies fully corroborate the unusual mechanism.

Results

During a Fischer synthesis of a pharmacologically active indole compound, *N*-(*p*-chlorobenzyl)-3-methyl-5-fluoroindole-2-α,α-dimethylpropionic acid,[5] formation of con-

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