Regioselectivity of Electrophilic Aromatic Substitution: Syntheses of 6- and 7-Sulfamoylindolines and -indoles

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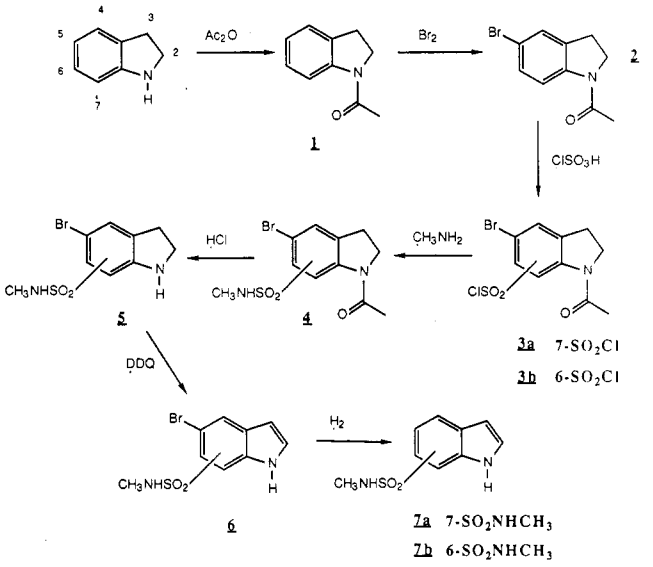
The previously reported chlorosulfonation of 1-acetyl-5-bromoindoline at the 7-position is in error. In actuality, the 6-substituted product is the sole regioisomer produced. This regiochemical assignment is based on NMR data and confirmed by X-ray analysis. We have prepared the first 7-sulfamoylindoline and the corresponding indole from indoline using the indoline nitrogen to direct sulfamoylation intramolecularly to the 7-position. The new 7-substituted derivatives may prove to be important as intermediates to indole-based dyes and as herbicides.

The two title isomeric indoles and the known 5-substituted isomer, all prepared from indoline, are important intermediates in the synthesis of Polaroid indolephthalein filter dyes.[1] 5- and 7-sulfamoyl-*N*-carbamylindolines have been reported to exhibit herbicidal activity.[2] The position of the sulfamoyl group on the indoline/indole ring has a profound affect on the properties of the herbicides and dyes containing that functionality. We sought to explore the effect of indole substitution on the physical characteristics of the filter dyes.

It has been reported[3a,b] that chlorosulfonation of 1-acetyl-5-bromoindoline (**2**) produces the 7-substituted sulfonyl chloride **3a** (Scheme I). This regiochemistry is consistent with that observed for nitration and bromination of **2**.[3c] However, we have found that chlorosulfonation of **2** actually occurs exclusively at the 6-position affording **3b** rather than **3a** as previously claimed. We have synthesized an authentic 7-sulfamoylindole **12** from indoline by an independent route.

Scheme I



Results and Discussion

In our initial attempts to synthesize 7-sulfamoylindoles, the previously reported chlorosulfonation of 1-acetyl-5-bromoindoline was utilized[3] (Scheme I). The sulfonyl chloride produced **3** was a single regioisomer which was reacted with methylamine to give the corresponding sulfonamide **4**, whose regiochemistry was at first assumed to be 7-substituted as claimed in the previous literature. Conversion of **4** to the monosubstituted indole **7** was straightforward as shown in Scheme I. High-field NMR splitting patterns were not definitive enough for us to unambiguously assign this regiochemistry. Since this regiochemistry had never been rigorously proven, we felt further investigations were warranted.

Analysis of the proton NMR spectrum before and after deacylation of 1-acetyl-5-bromoindoline reveals an upfield chemical shift displacement of the 7-H doublet from 7.9 to 6.4 ppm. This 1.5 ppm shift is primarily due to the elimination of the anisotropic deshielding effect on the 7-H by the acetyl group. Anisotropic deshielding in acetylated indolines is well-known,[4] as the acetyl group prefers the endo[5] conformation relative to the indoline phenyl ring.

Similar analysis of the proton NMR spectrum before and after deacylation of sulfonamide **4**, derived from chlorosulfonation of 1-acetyl-5-bromoindoline, revealed the same upfield shift displacement indicating that the 7-position was protonated rather than sulfamoylated and suggesting that the sulfamoyl group was occupying the 6-position. An X-ray crystal structure determination on indole **7b** unambiguously confirmed this regiochemical assignment.

† Author to whom inquiries regarding the X-ray crystallographic data should be directed.

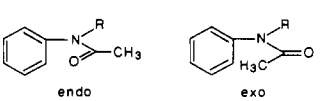
(1) Borror, A. L.; Chinoporos, E.; Petersen, C. P. U.S. Pat. 4 615 966, October 7, 1986.

(2) Hedrich, L. W.; Neighbors, R. P. U.S. Pat. 4 428 881, January 31, 1984.

(3) (a) Huyffer, P. S. U.S. Pat. 3 772 329, January 21, 1971. (b) Ikan, R.; Ikan, Y.; Fatal, Y. *J. Chem. Eng. Data* **1971**, *16*, 125. (c) Gall, W. G.; Astill, B. D.; Boekelheide, V. *J. Org. Chem.* **1955**, *20*, 1538.

(4) (a) Nagarajan, K.; Nair, M. D.; Pillai, P. M. *Tetrahedron* **1966**, *23*, 1683. (b) Jones, R. A. Y.; Katritzky, A. R.; Shapiro, B. B. *Tetrahedron* **1970**, *26*, 721.

(5) The terminology "endo" and "exo" has been generally used to describe the orientation of the acetyl carbonyl oxygen relative to the phenyl ring in anilides and *N*-acylindolines (see: Pedersen, B. F.; Pedersen, B. *Tetrahedron Lett.* **1965**, *34*, 2995, and references 4b and 10). "Endo" refers to the "cis" orientation and "exo" refers to the "trans" orientation.



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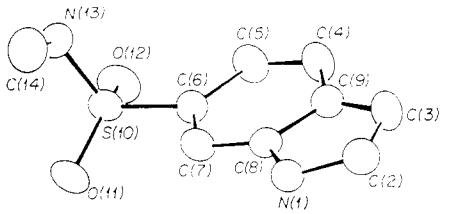


Figure 1. Perspective view of 6-(methylsulfamoyl)indole with numbering scheme. Hydrogen atoms have been omitted for clarity.

Scheme II. Synthesis of 7-(Methylsulfamoyl)indole

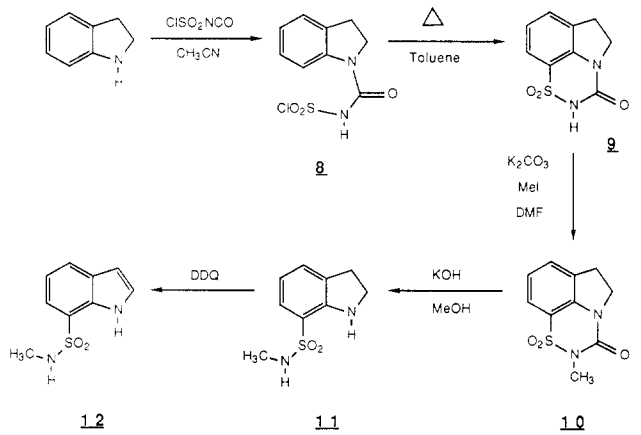
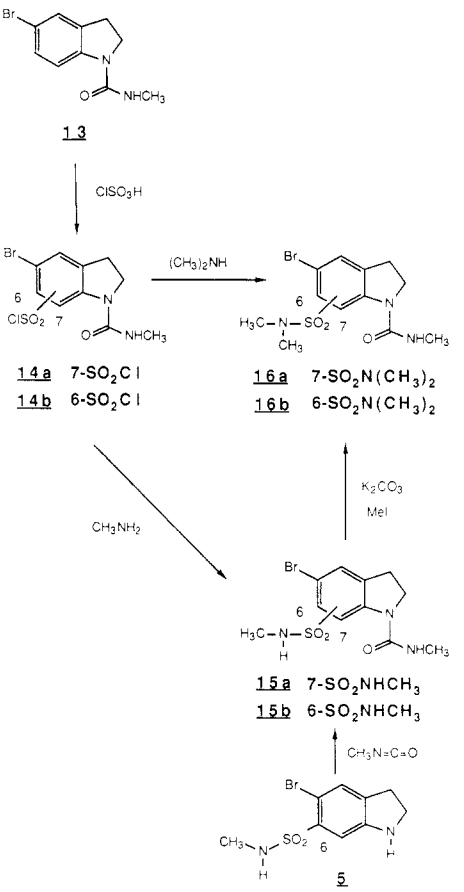


Figure 1 shows a perspective drawing of the final X-ray model of this indole. The bond lengths and angles agree well with generally accepted values, though the C(6)–C(7)–C(8) angle is rather small due to the electron-withdrawing effect of the sulfamoyl group at C(6).[6]

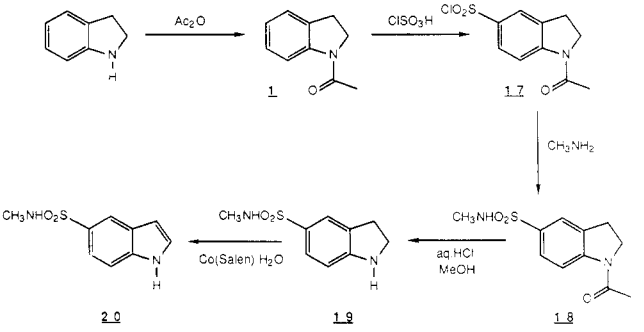
The indole skeleton of **7b** is nearly planar (maximum deviation 0.017 Å) but exhibits a slight folding about the ring junction. The *N*-methylsulfamoyl group is oriented to place the nitrogen atom approximately orthogonal to the plane of the indole skeleton (C(5)–C(6)–S(10)–N(13) –93.0 (1)° and C(7)–C(6)–S(10)–N(13) 83.6 (1)°). This places the oxygen atoms quite close to the ring (C(5)–C(6)–S(10)–O(12) 21.1 (2)° and C(7)–C(6)–S(10)–O(11) –31.3 (1)°). The valency angles about sulfur range from 105.6 (1) to 119.8 (1)° with the smallest being O–S–N angles and the largest being the O–S–O.[7]

An authentic sample of the 7-sulfamoylindole was prepared from indoline by reaction with chlorosulfonyl isocyanate followed by conversion of the *N*-(chlorosulfonyl)urea **8** to the cyclic urea **9**. Methylation and hydrolysis afforded indoline **11**, which was oxidized to the corresponding indole **12** (Scheme II). As expected, the physical, spectral, and chromatographic properties of 7-substituted indole **12** are distinctly different from those of the 6-substituted indole **7b**. Analogous procedures involving chlorosulfonyl isocyanate have been reported for the synthesis of 2-aminobenzenesulfonamides from anilines[8a] and benzothiadiazinone dioxides from 6-substituted

Scheme III



Scheme IV



2,3-diphenylindoles.[8b] We are unaware of any previous synthesis of a 7-sulfamoylindoline produced by this or any other route.

Based upon these results, we suspected that the herbicidally active **16**, purported to be *N*-(methylcarbamyl)-5-bromo-7-(dimethylsulfamoyl)indoline[2] (**16a**) is in fact the 6-sulfamoyl isomer **16b**. Chlorosulfonation of 5-bromo-*N*-(methylcarbamyl)indoline followed by reaction with dimethylamine did produce **16b** as a single sulfamoyl isomer whose NMR spectrum was consistent with 6-substitution rather than 7-substitution as claimed (Scheme III).

This regiochemistry was confirmed by reacting 5-bromo-6-(methylsulfamoyl)indoline (**5**) with methyl isocyanate to produce the corresponding urea **15b**. This same compound is produced via the Hedrich route when sulfonyl chloride **14b** is reacted with methylamine. Furthermore, tertiary sulfonamide **16b** is produced by methylation of secondary sulfonamide **15b**.

Chlorosulfonation of 1-acetylindoline is reported to give 1-acetyl-5-(chlorosulfonyl)indoline (**17**).[9] We utilized this

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(7) All crystallographic calculations were done on a VAX 11/780 computer. Principal programs used were MULTAN80, a system of computer programs for the automatic solution of crystal structures from X-ray diffraction data, P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, University of York, England, 1980; FMLS, P. L. Ganzel, R. A. Sparks, and K. N. Trueblood, UCLA (modified by A. T. McPhail, Duke University); ORTEP, crystallographic illustration program, ORNL-3794, C. K. Johnson, Oak Ridge, TN, 1976.

(8) (a) Girard, Y.; Atkinson, J. G.; Rokach, J. *J. Chem. Soc., Perkin. Trans. 1* **1979**, 1043. (b) Kamal, A.; Reddy, N.; Sattur, P. *Heterocycles* **1986**, *24*, 3397.

procedure to obtain 5-(methylsulfamoyl)indoline (**19**), which was oxidized to the corresponding indole **20** using Co(salen) (the cobalt complex of ethylenediaminesalicylaldehyde bis Schiff's base) in methanol (Scheme IV).[10] This oxidation is milder and cleaner than procedures employing quinone-type oxidants. As expected, the physical, spectral, and chromatographic properties of **20** are different from those of regioisomers **7b** and **12**. The proton NMR spectrum of **20** is quite similar to that of 5-bromoindole,[11] which strongly suggests that **20** is indeed substituted at carbon 5.

The chlorosulfonation of 1-acetyl-5-bromoindoline at the 6-position is not unique to indoline. We have found the "directing forces" in an analogous aniline to be the same as those in the indoline. Thus, chlorosulfonation of 4-bromo-2-methylacetanilide (**21**) gave only the 5-substituted sulfonyl chloride **22** (Scheme V). Conversion to the sulfonamide **23** and deacetylation produced the aniline **24**. We observed the expected anisotropic deshielding effect on the 6-H by the acetyl group in this aniline series. As in the indoline series, this effect is well-known with acetanilides.[12] It has been concluded from various studies that the preferred conformation of the acetyl group in acetanilide is endo, thus accounting for the observed anisotropic deshielding.

Further investigation may be necessary to fully rationalize our observation that, while chlorosulfonation of 1-acetyl-5-bromoindoline occurs at the 6-position, nitration or bromination occurs at the 7-position. One possible explanation involves complexation between chlorosulfonic acid and the acetamido functionality that would render the nitrogen meta-directing. Alternatively, the reactive electrophile in the chlorosulfonation reaction may simply be more sterically encumbered than that in nitration or bromination reactions and thus more prone to react at the less hindered 6-position.

Experimental Section

Melting points were determined on a Buchi melting point apparatus and are uncorrected. Unless otherwise noted, IR spectra were determined with a Perkin Elmer 727 B infrared recording spectrophotometer. The UV–vis spectra were recorded on a Varian Cary 2200 spectrophotometer. ^{1}H NMR were determined on the following spectrometers: Varian EM-390 or Varian XL300. All spectra were obtained in the solvents indicated and chemical shifts are expressed in ppm downfield from internal TMS. Significant ^{1}H NMR data are tabulated in order: multiplicity, relavent coupling constants, and number of protons. Mass spectra were recorded on a VG 7070 double focusing mass spectrometer with both EI and FAB$^+$ techniques. Thin layer chromatography was carried out on plates coated with silica gel, Whatman K5F, analytical 250 μm and preparative 1000 μm. Flash[13] column chromatographic separations were performed with silica gel, Woelm 32-63, Universal Scientific Incorporated, using nitrogen to provide elution pressure. Microanalyses were performed by Galbraith Laboratories. Exact mass determinations were obtained on a Kratos MS 50 double focusing mass spectrometer at Harvard University, Cambridge, MA.

5-Bromo-6-(chlorosulfonyl)-*N*-acetylindoline (3b). To 116.5 g (2.6 mol) of chlorosulfonic acid cooled in an ice bath was added 122.9 g (2.51 mol) of 5-bromo-*N*-acetylindoline (**2**) very cautiously over a period of 30 min. The mixture was stirred for 30 min at 0 °C, warmed to room temperature, and then heated to 70 °C for 8 h. The mixture was cooled and slowly poured onto ice and the solids were collected by suction filtration. The solids were washed several times with water and allowed to dry, and the product was recrystallized from chloroform and gave 72.5 g (42%) of 5-bromo-6-(chlorosulfonyl)-*N*-acetylindoline: mp 213–215 °C; IR (KBr) 1670, 1390 cm^{-1}; ^{1}H NMR (DMSO, 90 MHz) δ 8.55 (s, 1 H), 7.32 (s, 1 H), 4.01 (t, J = 8 Hz, 2 H), 3.03 (t, J = 8 Hz, 2 H), 2.09 (s, 3 H); MS, m/e 338. An analytical sample was recrystallized from chloroform. Anal. Calcd for $C_{10}H_9BrClNO_3S$: C, 35.46; H, 2.68; Br, 23.59; Cl, 9.47; N, 4.13; S, 9.47. Found: C, 35.67; H, 2.69; Br, 23.25; Cl, 10.78; N, 4.09; S, 9.73.

5-Bromo-6-(methylsulfamoyl)-*N*-acetylindoline (4). To a suspension of 71.8 g (0.212 mol) of 5-bromo-6-(chlorosulfonyl)-*N*-acetylindoline (**3b**) in 600 mL of tetrahydrofuran was added 32.9 mL (0.424 mol) of a 40% solution of methylamine in water and 61.1 mL (0.424 mol) of triethylamine. The mixture was heated to reflux for 1.5 h and then allowed to cool. It was concentrated under reduced pressure and the resulting solid was suspended in hot methanol, filtered, washed with methanol, and allowed to dry to give 65.1 g (92%) of 5-bromo-6-(methylsulfamoyl)-*N*-acetylindoline: mp 218.5–220 °C; IR (KBr) 1640, 1570, 1320 cm^{-1}; ^{1}H NMR (DMSO, 90 MHz) δ 8.66 (s, 1 H), 7.63 (s, 1 H), 7.47 (m, 1 H), 4.13 (t, J = 8 Hz, 2 H), 3.18 (t, J = 8 Hz, 2 H), 2.44 (br s, 3 H), 2.15 (s, 3 H); MS, m/e 333. An analytical sample was recrystallized from methanol. Anal. Calcd for $C_{11}H_{13}BrN_2O_3S$: C, 39.65; H, 3.93; Br, 23.98; N, 8.40; S, 9.62. Found: C, 39.76; H, 3.97; Br, 23.72; N, 8.33; S, 9.75.

5-Bromo-6-(methylsulfamoyl)indoline (5). To a stirred suspension of 65.1 g (0.196 mol) of 5-bromo-6-(methylsulfamoyl)-*N*-acetylindoline (**4**) in 200 mL of dioxane was added 146 mL (1.75 mol) of concentrated hydrochloric acid. The mixture was stirred and refluxed for 1.5 h and allowed to cool. It was concentrated under reduced pressure, cooled in an ice bath, and neutralized with 10% sodium hydroxide solution to pH 7. The resulting white precipitate was filtered, washed several times with water, and dried to give 55.9 g (98%) of 5-bromo-6-(methylsulfamoyl)indoline: mp 161–162 °C; IR (KBr) 3315, 1330, 850 cm^{-1}; ^{1}H NMR (DMSO, 90 MHz) δ 7.29 (s, 1 H), 7.17 (m, 1 H), 6.98 (s, 1 H), 3.45 (t, J = 7.5 Hz, 2 H), 3.26 (br m, 1 H), 2.92 (t, J = 7.5 Hz, 2 H), 2.37 (d, J = 1.5 Hz, 3 H); MS, m/e 291. An analytical sample was recrystallized from ethanol. Anal. Calcd for $C_9H_{11}BrN_2O_2S$: C, 37.12; H, 3.80; Br, 27.44; N, 9.62; S, 11.01. Found: C, 37.34; H, 3.93; Br, 27.25; N, 9.62; S, 11.08.

5-Bromo-6-(methylsulfamoyl)indole (6). To a stirred solution of 55.9 g (0.19 mol) of 5-bromo-6-(methylsulfamoyl)indoline (**5**) in 150 mL of dioxane was added 41.8 g (0.184 mol) of 2,3-dichloro-5,6-dicyanobenzoquinone at 25 °C. The resulting solution was heated to 80 °C for 2 h and allowed to cool. The slurry was filtered through Celite and the filtrate was concentrated under reduced pressure. The resulting brown solid was stirred in a 1:1 mixture of methylene chloride/ether and then filtered. This procedure was carried out two additional times and gave 35.2 g (63.9%) of the indole: mp 203–204 °C; IR (KBr) 3350, 1340, 650 cm^{-1}; ^{1}H NMR (DMSO, 90 MHz) δ 8.15 (s, 1 H), 7.98 (s, 1 H), 7.64 (t, J = 3 Hz, 1 H), 7.24 (q, J = 5.5 Hz, 1 H), 6.51 (m, 1 H), 2.43 (d, J = 5.5 Hz, 1 H); MS, m/e 289. An analytical sample was obtained by preparative thin-layer chromatography (silica gel eluted with 2% methanol in methylene chloride). Anal. Calcd for $C_9H_9BrN_2O_2S$: C, 37.38; H, 3.14; Br, 27.63; N, 9.69; S, 11.06. Found: C, 37.17; H, 3.34; Br, 27.63; N, 9.59; S, 11.24.

6-(Methylsulfamoyl)indole (7b). To a solution of 8.68 g (0.299 mol) of 5-bromo-6-(methylsulfamoyl)indole (**6**) in 50 mL of ethanol that had been degassed with nitrogen for 15 min was added 5.0 mL (0.36 mol) of triethylamine followed by 1.09 g of 10% palladium on carbon. The mixture was hydrogenated (40 psig) for 3 h. The slurry was filtered and concentrated under reduced pressure and the remaining oil was purified by chromatography (silica gel eluted with 2.5% methanol in methylene chloride) and gave 5.76 g (91%) of the indole: mp 98–99.5 °C; TLC R_f 0.33 (2.5% methanol in methylene chloride); IR (KBr) 3380, 3255, 1345, 825 cm^{-1}; UV (95% ethanol) λ_{max} 230 nm (log ϵ 4.58); ^{1}H NMR (DMSO, 300 MHz) δ 7.86 (m, J = 2.4 Hz, 1 H), 7.73 (d, J = 8.40 Hz, 1 H), 7.63 (t, J = 3.0 Hz, 1 H), 7.39 (dd, J = 8.40, 2.40 Hz, 1 H), 7.25 (q, J = 4.5 Hz, 2 H), 6.57 (t, J = 3.0 Hz, 1 H), 2.37 (d, J = 4.5 Hz, 3 H); MS, m/e 210. An analytical sample was obtained by thin-layer chromatography (silica gel eluted with 2% methanol in methylene chloride). Anal. Calcd

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(10) Inada, A.; Nakamura, Y.; Morita, Y. *Chem. Lett.* **1980**, 1287.
(11) Saito, K.; Kikugawa, Y. *J. Heterocycl. Chem.* **1979**, *16*, 1325.
(12) Carter, R. *Acta Chem. Scand.* **1967**, *21*, 75.
(13) Still, W.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.79; N, 13.33; S, 15.29. Found: C, 51.42; H, 5.07; N, 13.28; S, 15.38.

N-((Chlorosulfonyl)carbamyl)indoline (8). Chlorosulfonyl isocyanate, 3.76 g (26.7 mmol), in 20 mL of dry acetonitrile was added dropwise over a period of 30 min to a mechanically stirred solution of 3.18 g (26.7 mmol) of indoline in acetonitrile at 0 °C under an atmosphere of dry nitrogen. After an additional 30 min, the reaction was allowed to stand overnight to allow product crystallization. Diethyl ether (30 mL) was added and the product collected by suction filtration under an inverted funnel of nitrogen. It was washed with diethyl ether (2×50 mL), dried under vacuum, and gave 5.13 g (74%) of product as a fluffy white solid: mp 136-137 °C dec; IR (KBr) 3390, 3180, 1660 cm^{-1}; ^1H NMR (DMSO/$CDCl_3$) δ 7.71 (d, J = 7 Hz, 1 H), 7.30–6.80 (m, 3 H), 3.97 (t, J = 8 Hz, 2 H), 3.13 (t, J = 8 Hz, 2 H); MS, m/e 260. The compound was converted to the corresponding urea by hydrolysis in aqueous acetone. An analytical sample was recrystallized from benzene (mp 161–162 °C). Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.49; H, 6.23; N, 17.22.

2,3,5,6-Tetrahydropyrrolo[1,2,3-*de*]-1,2,4-benzothiadiazin-3-one 1,1-Dioxide (9). A slurry of 15.2 g (58.5 mmol) of N-(chlorosulfonyl)urea **8** in 500 mL of dry toluene was slowly heated to reflux. The mixture became homogeneous and then cloudy as the product began to precipitate. It was heated under gentle reflux for 4 h and allowed to cool, and the resulting off-white solid was collected by suction filtration. This gave 3.07 g (23%) of the final compound: mp 255–260 °C; IR (KBr) 3100, 3000, 1665, 1620, 1590 cm^{-1}; UV (95% ethanol) λ_{max} 213 nm (log ϵ 4.32); ^1H NMR δ (DMSO, 90 MHz) δ 7.70–7.30 (m, 2 H), 7.10 (t, J = 7 Hz, 3 H), 4.03 (t, J = 9 Hz, 2 H), 3.20 (t, J = 9 Hz, 2 H); MS, m/e 224. Anal. Calcd for $C_9H_8N_2O_3S$: C, 48.21; H, 3.60; N, 12.49; S, 14.30. Found: C, 47.95; H, 3.90; N, 12.14; S, 14.80.

2,3,5,6-Tetrahydropyrrolo[1,2,3-*de*]-2-methyl-1,2,4-benzothiadiazin-3-one 1,1-Dioxide (10). To a slurry of 0.373 g (1.67 mmol) of cyclic urea **9** and 2.28 g (16.1 mmol) of methyl iodide in 2 mL of acetone and 1 mL of dimethylformamide was added 0.2 g (1.45 mmol) of finely powdered potassium carbonate. After stirring 72 h at room temperature, the reaction was poured into dilute hydrochloric acid (25 mL) and extracted with chloroform (3 × 50 mL). The combined chloroform layers were washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting crystalline material was purified by flash chromatography (silica gel eluted with 2% methanol in methylene chloride) and gave 0.31 g (78%) of white crystalline material: mp 162–163 °C; IR (KBr) 1690, 1620, 1590 cm^{-1}; UV (95% ethanol) λ_{max} 216 nm (log ϵ 4.31); ^1H NMR δ ($CDCl_3$, 90 MHz) 7.57 (d, J = 7 Hz, 1 H), 7.44 (d, J = 7 Hz, 1 H), 7.11 (t, J = 7 Hz, 1 H), 4.25 (t, J = 9 Hz, 2 H), 3.33 (t, J = 9 Hz, 2 H), 3.33 (s, 3 H); MS, m/e 238. An analytical sample was recrystallized from methanol. Anal. Calcd for $C_{10}H_{10}N_2O_3S$: C, 50.41; H, 4.23; N, 11.76; S, 13.46. Found: C, 50.10; H, 4.29; N, 11.67; S, 13.78.

7-(Methylsulfamoyl)indoline (11). To a mixture of 100 mL of methanol and 50 mL of a 10% aqueous solution of potassium hydroxide at room temperature was added 0.7 g (2.94 mmol) of the cyclic sulfonylurea **10**. The resulting mixture was stirred for 24 h and then concentrated under reduced pressure. The aqueous suspension was taken to pH 7 with dilute hydrochloric acid and then extracted with methylene chloride (3 × 50 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated under reduced pressure, and gave 0.63 g (quantitative yield) of product as white needles: mp 118–119 °C; IR (KBr) 3400, 3250, 1602, 1578 cm^{-1}; UV (95% ethanol) λ_{max} 215 nm (log ϵ 4.24); ^1H NMR δ ($CDCl_3$, 90 MHz) 7.61 (t, J = 7 Hz, 1 H), 7.32 (d, J = 7 Hz, 1 H), 7.18 (d, J = 7 Hz, 1 H), 5.33 (br s, 1 H), 4.55 (br s, 1 H), 3.64 (t, J = 7 Hz, 2 H), 3.06 (t, J = 7 Hz, 2 H), 2.60 (d, J = 6 Hz, 3 H); MS, m/e 212. An analytical sample was recrystallized from a 95/5 mixture of water/ethanol. Anal. Calcd for $C_6H_{12}N_2O_2S$: C, 50.93; H, 5.70; N, 13.20; S, 15.11. Found: C, 50.83; H, 5.80; N, 13.02; S, 15.13.

7-(Methylsulfamoyl)indole (12). To a stirred solution of 1.16 g (5.50 mmol) of indoline **11** in 75 mL of methylene chloride at room temperature was added 1.35 g (5.50 mmol) of 2,3-dichloro-5,6-dicyanobenzoquinone in one portion. A rapid reaction ensued, followed by precipitation of byproducts. After 1 h the mixture was filtered through Celite, concentrated, and purifed by chromatography (silica gel eluted with 3% methanol in methylene chloride) and gave 0.95 g (82%) of analytically pure product: mp 63–67 °C; TLC R_f 0.69 (2.5% methanol in methylene chloride); IR (KBr) 3400, 3280, 1602, 1570 cm^{-1}; UV (95% ethanol) λ_{max} 224 nm (log ϵ 4.37); ^1H NMR δ (90 MHz) 9.68 (br s, 1 H), 7.91 (d, J = 7 Hz, 1 H), 7.67 (d, J = 7 Hz, 1 H), 7.35 (t, J = 2 Hz, 1 H), 7.24 (t, J = 7 Hz, 1 H), 6.67 (t, J = 2 Hz, 1 H), 4.95 (q, J = 6 Hz, 1 H), 2.63 (d, J = 6 Hz, 3 H); MS, m/e 210. Anal. Calcd for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.79; N, 13.32; S, 15.25. Found: C, 51.56; H, 4.91; N, 13.12; S, 15.62.

5-Bromo-6-(chlorosulfonyl)-N-(methylcarbamyl)indoline (14b). To an ice-cooled flask containing 3.7 mL (55 mmol) of chlorosulfonic acid was added 3.0 g (11.7 mmol) of 5-bromo-N-methylcarbamylindoline (**13**) in several portions over a 10-min period. The resulting mixture was heated to 65 °C for 2 h, cooled, and poured into ice water. It was filtered, washed several times with water, allowed to dry and gave 2.8 g (68%) of the indoline: mp 211–212.5 °C; IR (KBr) 1670, 1540, 1380 cm^{-1}; ^1H NMR (DMSO, 90 MHz) δ 8.34 (s, 1 H), 7.19 (s, 1 H), 3.77 (t, J = 9 Hz, 2 H), 2.99 (t, J = 9 Hz, 2 H), 2.58 (br s, 3 H); exact mass calcd for $C_{10}H_{10}N_2O_3SBrCl$ 351.9284, found 351.9287.

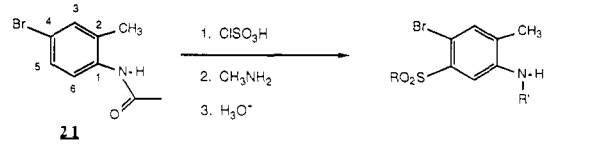
5-Bromo-6-(methylsulfamoyl)-N-(methylcarbamyl)indoline (15b). To an ice-cooled solution of 1.0 g (3.0 mmol) of 5-bromo-6-(methylsulfamoyl)indoline (**5**) and 0.46 mL (3.3 mmol) of triethylamine in 25 mL of tetrahydrofuran was added dropwise over a 5-min period a solution of 0.19 mL (3.3 mmol) of methyl isocyanate in 0.5 mL of tetrahydrofuran. The solution was heated 4.5 h and cooled and solvent was removed under reduced pressure. The resulting solid was triturated with water, dried, and recrystallized from methanol to give 0.45 g (43%) of product: mp 241 °C; IR (KBr) 3220, 1675, 1540, 1345 cm^{-1}; ^1H NMR (DMSO, 300 MHz) δ 8.44 (s, 1 H), 7.48 (s, 1 H), 7.37 (q, J = 3.0 Hz, 1 H), 6.69 (q, J = 5 Hz, 1 H), 3.86 (t, J = 9 Hz, 2 H), 3.12 (t, J = 9 Hz, 2 H), 2.63 (d, J = 5 Hz, 3 H), 2.41 (t, J = 3.0 Hz, 3 H); MS, m/e 348. An analytical sample was recrystallized from methanol. Anal. Calcd for $C_{11}H_{14}N_3O_3SBr$: C, 37.95; H, 4.05; N, 12.07; S, 9.19; Br, 22.95. Found: C, 38.29; H, 3.97; N, 12.05; S, 9.47; Br, 23.34.

5-Bromo-6-(methylsulfamoyl)-N-(methylcarbamyl)indoline (15b) from 5-Bromo-6-(chlorosulfonyl)-N-(methylcarbamyl)indoline (14b). To a stirred solution of 2.0 g (5.65 mmol) of compound **14b** in 50 mL of tetrahydrofuran was added 0.87 mL (11.3 mmol) of a 40% aqueous solution of methylamine and 1.63 mL (11.3 mmol) of triethylamine. The mixture was refluxed for 2 h, cooled, and concentrated under reduced pressure. The resulting solid was slurried in hot methanol and filtered to give 0.9 g (46%) of the indoline. This compound exhibited identical NMR, mp, MS and TLC behavior with that of compound **15b** described above.

5-Bromo-6-(dimethylsulfamoyl)-N-(methylcarbamyl)indoline (16b). To a stirred solution of 0.2 g (0.57 mmol) of 5-bromo-6-(methylsulfamoyl)-N-(methylcarbamyl)indoline (**15b**) in 10 mL of tetrahydrofuran at 25 °C was added 0.068 g (0.6 mmol) of potassium *tert*-butoxide. After 10 min, 0.65 mL (10.5 mmol) of methyl iodide was added and the mixture was allowed to stir for 30 h. The solvent was removed under reduced pressure, and the residue was dissolved in 10 mL of methylene chloride and washed with water (2 × 10 mL) and saturated sodium chloride (2 × 10 mL) and dried over sodium sulfate. It was filtered, concentrated under reduced pressure, and purified by preparative chromatography (silica gel eluted with 2% methanol in methylene chloride) to give 0.18 g (88%) of product: mp 203–203.5 °C; IR (KBr) 3170, 1645, 1340 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 8.42 (s, 1 H), 7.33 (s, 1 H), 4.6 (br m, 1 H), 3.84 (t, J = 8.5 Hz, 2 H), 3.15 (t, J = 8.5 Hz, 2 H), 2.84 (s, 6 H), 2.81 (br s, 3 H); MS, m/e 362. An analytical sample was recrystallized from ethanol/water. Anal. Calcd for $C_{12}H_{16}N_3O_3SBr$: C, 39.79; H, 4.45; N, 11.60; S, 8.84; Br, 22.06. Found: C, 39.71; H, 4.33; N, 11.55; S, 9.22; Br, 22.23.

5-Bromo-6-(dimethylsulfamoyl)-N-(methylcarbamyl)indoline (16b) from 5-Bromo-6-(chlorosulfonyl)-N-(methylcarbamyl)indoline (14b). To a stirred solution of compound **14b** in 15 mL of tetrahydrofuran at 25 °C was added 0.5 mL (2.8 mmol) of a 25% aqueous solution of dimethylamine and 0.37 mL (2.8 mmol) of triethylamine. The mixture was refluxed for 2.5 h, allowed to cool, and concentrated under reduced pressure. The resulting solid was slurried in hot methanol, filtered, purified by

Scheme V



21

22 R=Cl R' =$COCH_3$
23 $R=CH_3NH$ R' =$COCH_3$
24 $R=CH_3NH$ R' =H

flash chromatography (silica gel eluted with 2% methanol in methylene chloride), and gave 0.4 g (79%) of product. The compound exhibited identical NMR, mp, MS, and TLC behavior with that of compound **16b** described above.

5-(Chlorosulfonyl)-*N*-acetylindoline (17). To 160 mL (2.4 mol) of chlorosulfonic acid cooled in an ice bath was added 77 g (0.48 mol) of *N*-acetylindoline (1) portionwise over a period of 30 min. The mixture was warmed to room temperature and then heated to 70 °C for 45 min. It was cooled and poured onto ice and the solids were collected by suction filtration, washed several times with water, and allowed to dry. The product was recrystallized from 2-propanol and gave 107 g (86%) of the sulfonyl chloride: mp 167–169 °C (lit.[8] mp 170–171 °C); IR (KBr) 1670, 1380, 1160 cm^{-1}; ^1H NMR (DMSO, 90 MHz) δ 7.93 (br s, J = 9 Hz, 1 H), 7.41 (br s, 1 H), 7.33 (br s, 1 H), 4.02 (t, J = 8 Hz, 2 H), 3.03 (t, J = 8 Hz, 2 H), 2.09 (s, 3 H); MS, m/e 260.

5-(Methylsulfamoyl)-*N*-acetylindoline (18). To a suspension of 35 g (0.135 mol) of 5-(chlorosulfonyl)-*N*-acetylindoline (17) in 100 mL of methylene chloride at 0 °C was added 32 mL (0.27 mol) of a 40% aqueous solution of methylamine and 40 mL (0.27 mol) of triethylamine. The solution was warmed to room temperature and then refluxed for 2.5 h. It was cooled, and solvent removed under reduced pressure. The white pasty product was triturated with a dilute solution of hydrochloric acid, filtered by suction filtration, and washed with water. It was then slurried in methanol, filtered, dried, and gave 30.3 g (88%) of the sulfonamide: mp 211–212 °C; IR (KBr) 1650, 1340 cm^{-1}; ^1H NMR (DMSO, 90 MHz) δ 8.08 (d, J = 9 Hz, 1 H), 7.52 (m, 2 H), 7.19 (q, J = 5 Hz, 2 H), 4.08 (t, J = 8.5 Hz, 2 H), 3.12 (t, J = 8.5 Hz, 2 H), 2.33 (d, J = 5 Hz, 3 H), 2.13 (s, 3 H); MS, m/e 254. An analytical sample was recrystallized from methanol. Anal. Calcd for $C_{11}H_{14}N_2O_3S$: C, 51.95; H, 5.55; N, 11.02; S, 12.61. Found: C, 51.94; H, 5.60; N, 10.97; S, 12.67.

5-(Methylsulfamoyl)indoline (19). To a suspension of 16.0 g (62.9 mmol) of 5-(methylsulfamoyl)-*N*-acetylindoline (18) in 150 mL of methanol was added 26 mL (0.315 mol) of concentrated hydrochloric acid. The mixture was refluxed for 1.5 h and cooled, and solvent was removed under reduced pressure. The pasty product was dissolved in water and the solution was adjusted to pH 7 with 1 N sodium hydroxide. The precipitate was collected by suction filtration, washed several times with water, and gave 11.9 g (89%) of product: mp 123–124 °C; IR (KBr) 1605, 1290 cm^{-1}; ^1H NMR (DMSO, 90 MHz) δ 7.28 (m, 1 H), 7.24 (m, 1 H), 6.77 (q, J = 5.5 Hz, 1 H), 6.44 (d, J = 9 Hz, 1 H), 6.15 (m, 1 H), 3.46 (t, J = 8.5 Hz, 2 H), 2.88 (t, J = 8.5 Hz, 2 H), 2.32 (d, J = 5.5 Hz, 3 H); MS, m/e 212. An analytical sample was recrystallized from methylene chloride and hexane. Anal. Calcd for $C_9H_{12}N_2O_2S$: C, 50.93; H, 5.70; N, 13.20; S, 15.11. Found: C, 50.77; H, 5.43; N, 13.21; S, 15.10.

5-(Methylsulfamoyl)indole (20). To a solution of 5 g (23.6 mmol) of 5-(methylsulfamoyl)indoline (19) in 25 mL of methanol was added 0.54 g (1.57 mmol) of Co(salen) hydrate. Air was bubbled through the solution at 25 °C for 24 h. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel eluted with 3/1 mixture of hexane/acetone) and gave 4.21 g (85%) of indole: mp 146–147 °C; TLC R_f 0.51 (2.5% methanol in methylene chloride); UV (95% ethanol) λ_{max} 230 nm (log ϵ 4.79); IR (KBr) 3465, 3250, 1290, 1145 cm^{-1}; ^1H NMR (DMSO, 90 MHz) δ 8.07 (s, 1 H), 7.53 (m, 3 H), 7.15 (q, 1 H), 6.65 (m, 1 H), 2.35 (d, 3 H); MS, m/e 210. An analytical sample was recrystallized from a mixture of methylene chloride and hexane. Anal. Calcd for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.80; N, 13.32; S, 15.25. Found: C, 51.39; H, 4.64; N, 13.36; S, 15.29.

4-Bromo-2-methylacetanilide (21). To a chilled solution of 12.0 g (64.5 mmol) of 4-bromo-2-methylaniline in 50 mL of methylene chloride was added 18.6 mL (0.13 mol) of triethylamine. The solution was cooled to 0 °C and 12.2 mL (0.13 mol) of acetic anhydride was added over a 10-min period. The mixture was allowed to warm to room temperature, washed with water (3 × 50 mL) and saturated sodium chloride (2 × 50 mL), and dried over sodium sulfate. It was filtered and concentrated under reduced pressure and gave 14.0 g (96%) of acetanilide **21**: mp 158–159 °C; IR (KBr) 1720, 1545, 1290 cm^{-1}; ^1H NMR (DMSO, 90 MHz) δ 9.34 (br s, 1 H), 7.40 (br s, 3 H), 2.20 s, 3 H), 2.05 (s, 3 H); MS, m/e 228. An analytical sample was recrystallized from methanol. Anal. Calcd for $C_9H_{10}BrNO$: C, 47.39; H, 4.42; Br, 35.03; N, 6.14. Found: C, 47.31; H, 4.59; Br, 34.66; N, 6.06.

4-Bromo-3-(chlorosulfonyl)-6-methylacetanilide (22). To 5.8 mL (87.5 mmol) of chlorosulfonic acid at 0 °C was added 4.0 g (17.5 mmol) of 4-bromo-2-methylacetanilide (**21**) portionwise over a 20-min period. The solution was warmed to room temperature and then heated to 60 °C for 2 h. The reaction was cooled and poured cautiously over 1 L of ice, and the precipitate was collected by suction filtration to give 3.1 g (54%) of the sulfonyl chloride: mp 135–136.5 °C; IR (KBr) 1660, 1515, 1375 cm^{-1}; ^1H NMR (DMSO, 90 MHz) δ 9.37 (br s, 1 H), 7.88 (s, 1 H), 7.37 (s, 1 H), 2.12 (s, 3 H), 2.02 (s, 3 H); exact mass calcd for $C_9H_9NO_3SBrCl$ 326.9151, found 326.9150.

4-Bromo-3-(methylsulfamoyl)-6-methylacetanilide (23). To a solution of 2 g (6.1 mmol) 4-bromo-3-(chlorosulfonyl)-2-methylacetanilide (**22**), in 10 mL of methylene chloride was added 1.8 mL (12.2 mmol) of triethylamine and 1.4 mL (12.2 mmol) of a 40% aqueous solution of methylamine in several portions over a 15-min period. The solution was warmed to room temperature and then refluxed for 1.25 h. After cooling, the organic layer was separated, washed with water (3 × 25 mL), dilute hydrochloric acid (25 mL), and saturated sodium chloride (50 mL). It was dried over sodium sulfate, filtered, and concentrated under reduced pressure to give 1.2 g (60%) of the sulfonamide product: mp 229.5–230.5 °C; IR (KBr) 1645, 1520, 1160 cm^{-1}; ^1H NMR (DMSO, 90 MHz) δ 9.38 (br s, 1 H), 8.12 (s, 1 H), 7.54 (s, 1 H), 7.39 (q, J = 5 Hz, 1 H), 2.31 (d, J = 5 Hz, 3 H), 2.10 (s, 3 H), 1.91 (s, 3 H); MS, m/e 321. An analytical sample was recrystallized from methanol. Anal. Calcd for $C_{10}H_{13}BrN_2O_3S$: C, 37.40; H, 4.08; Br, 24.88; N, 8.72; S, 9.98. Found: C, 37.48; H, 4.03; Br, 24.75; N, 8.61; S, 10.32.

4-Bromo-3-(methylsulfamoyl)-6-methylaniline (24). To a solution of 1.8 g (5.6 mmol) of 4-bromo-3-(methylsulfamoyl)-6-methylacetanilide (**23**) in 15 mL of methanol was added 2.3 mL (28 mmol) of concentrated hydrochloric acid. The solution was refluxed for 4 h, cooled, and concentrated under reduced pressure. The residue was dissolved in water and the solution adjusted to pH 7 with 1 N sodium hydroxide. The precipitate was collected by suction filtration, washed with water, and dried to give 1.4 g (90%) of the substituted aniline: mp 132–133 °C; IR (KBr) 1625, 1475 cm^{-1}; ^1H NMR (DMSO, 300 MHz) δ 7.33 (s, 1 H), 7.32 (s, 1 H), 7.03 (q, J = 4.5 Hz, 1 H), 5.33 (br s, 1 H), 2.43 (d, J = 4.5 Hz, 3 H), 2.10 (s, 3 H). An analytical sample was recrystallized from chloroform. Anal. Calcd for $C_8H_{11}BrN_2O_2S$: C, 34.42; H, 3.97; Br, 28.62; N, 10.04; S, 11.49. Found: C, 34.42; H, 3.92; Br, 28.49; N, 10.00; S, 11.83.

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Registry No. 1, 16078-30-1; 2, 22190-38-1; 3b, 107144-42-3; 4, 107144-43-4; 5, 113162-38-2; 6, 107144-44-5; 7b, 113180-44-2; 8, 89731-80-6; 9, 113162-39-3; 10, 113162-40-6; 11, 113162-41-7; 12, 113180-45-3; 13, 62368-16-5; 14b, 113162-42-8; 15b, 113162-43-9; 16b, 113162-44-0; 17, 52206-05-0; 18, 113162-45-1; 19, 113162-46-2;

20, 107144-39-8; 21, 24106-05-6; 22, 113162-47-3; 23, 113162-48-4; 24, 113162-49-5; $MeNH_2$, 74-89-5; $ClSO_2NCO$, 1189-71-5; MeNCO, 624-83-9; $HNMe_2$, 124-40-3; 2-Me-4-$BrC_6H_3NH_2$, 583-75-5; indoline, 496-15-1; 1-carbamoylindoline, 56632-33-8.

Supplementary Material Available: Tables of fractional atomic positional parameters, thermal parameters, interatomic distances and angles, and torsion angles for **7b** (6 pages). Ordering information is given on any current masthead page.

An Efficient Synthesis of Arylpyrazines and Bipyridines

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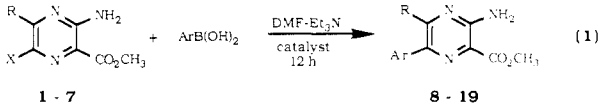
The coupling of chloro or bromo pyrazines and pyridines with areneboronic acids in the presence of palladium(0) catalysts is described. By use of the appropriate catalyst, the coupling of pyridineboronic acids was achieved. A convergent synthesis of the previously unknown 4-methyl derivative of the cardiotonic milrinone (**31**) is also described.

Substituted pyrazines occur widely in nature and are valuable heterocyclic nuclei for the design of pharmaceutical agents. In connection with our interest in the pyrazine congeners of the bipyridine cardiotonics amrinone and milrinone,[1-5] we examined the palladium(0)-catalyzed coupling reaction of areneboronic acids with 6-halo-2-aminopyrazinoate esters.[6,7] We report here that in the presence of [1,1'-bis(diphenylphosphino)ferrocene]palladium,[8] the method is generally useful for introducing substituted aryl and heteroaryl substituents, including the 3- and 4-pyridyl ring systems.[9] The utility of the method was further demonstrated as the key step in the synthesis of the novel 4-methyl derivative of milrinone.[10]



(1)

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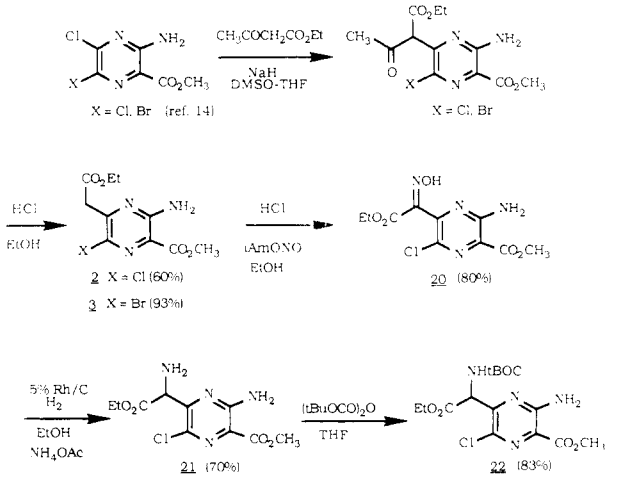
The results from a variety of 2-amino-6-halopyrazinoates are summarized in Table I. The 6-bromopyrazinoate **1** underwent conversion to the 6-phenylpyrazinoate[8] utilizing the conditions employed for the synthesis of arylpyridines.[8] However, only traces of the coupled products **13-17** were obtained when the 6-halo-5-substituted-pyrazinoates **2** and **3** were used as starting materials. Substituting the more stable bis(tri-*o*-tolylphosphine)-ligated palladium catalyst ($Pd(totp)(OAc)_2$) for the tetrakis(triphenylphosphine)-palladium catalyst ($Pd(PPh)_4$) did not afford much improvement. We then found that the binuclear catalyst, 1,1'-bis(diphenylphosphino)ferrocene-ligated palladium ($Pd(dppf)(OAc)_2$)[9] formed in situ, was significantly more effective in promoting the desired transformation. One explanation to account for the greater efficiency of the $Pd(dppf)_2(OAc)_2$ catalyst relative to the others might be the decreased steric hindrance enforced by the rigid ferrocene backbone which acts to "stretch" the Pd-P bond distance from its usual length.[8] The catalyst was also found to be successful for 4-fluorobenzene-, 4-methoxybenzene-, 3-furan-, 2-furan-, 3-thianaphthylene-, and 3- and 4-pyridineboronic acids with 6-bromopyrazinoates as shown in Table I.[20]

The less reactive 6-chloropyrazinoates **2**, **4**, and **6** also underwent the coupling reaction with the $Pd(dppf)_2(OAc)_2$ catalyst, although a slower rate of conversion was observed

Scheme I. Preparation of Methyl 3-Amino-5-alkyl-6-halopyrazinoates



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