Formamidines in Synthesis. An Efficient One-Pot Synthesis of 7-Substituted Indolines via Intramolecular Cyclization of (2-Phenethyl)formamidines. An Asymmetric Route to Benzopyrrocoline Alkaloids

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Received January 27, 1992

o-Chloro-β-phenethylamines, transformed into the *N*-*tert*-butylformamidines, were found to be excellent precursors to indolines following benzyne formation. A series of methoxy-substituted *o*-chlorophenethylamines containing an N-alkyl or aryl substitutent were subjected to *sec*-butyllithium producing the ortho-lithiated aromatic which subsequently lost lithium chloride at temperatures ranging from −78 to −50 °C. The resulting benzyne was intramolecularly trapped providing the titled heterocycles. Quenching the reaction resulted in elimination of the *tert*-butyl isocyanide (isolated after aqueous workup as *tert*-butylformamide) and protonation (or alkylation) of the 7-lithio position. Overall the yields for this process were 60–95% for a variety of N-substituted phenethylamines. In addition, a one-pot total asymmetric route to benzopyrrocoline alkaloids was featured using this benzyne trapping of chiral formamidines.

The synthesis of the indoline ring system has been of key interest to chemists for over a century due to their presence in a wide variety of materials.[1] Traditional approaches to indolines, in addition to the Fischer indole synthesis,[2] include metal-catalyzed couplings,[3] cycloadditions,[4] and a variety of intramolecular cyclizations[5] including amino groups adding to benzynes.[6,7]

During the course of evaluating the rich chemistry of formamidines in achiral[8] and chiral[9] molecules, we had the occasion to prepare the benzyne derivative of **1**, which had been shown earlier by others[6,7] to undergo the intramolecular process resulting in the indoline system **3**. However, these earlier studies required large excess of base, gave generally poor yields, and produced a number of side products. Because of this we were prompted to reassess the benzyne derived from **1**, using a "protected" nitrogen in the form of the *N*-*tert*-butylformamidine, **2**.[10] To our surprise, treatment of **2** with 2.0 equiv of *sec*-butyllithium (−78 °C, THF) followed by aqueous workup gave the *N*-methylindoline **3** (E = H) in quantitative yield. Thus, the N-Me group in the formamidine moiety served as a suitably placed nucleophile in **4** which added across the benzyne furnishing the 7-lithio derivative **5**. It is interesting that a tertiary amine acts as a nucleophile while the lithium chloride serves as the electrophilic partner in this process. Presumably other metal salts would behave in

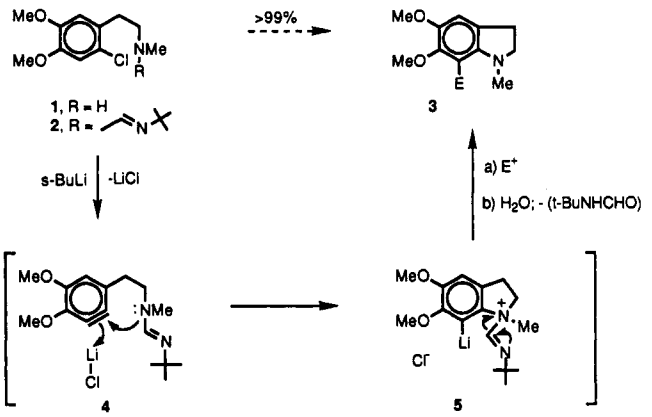
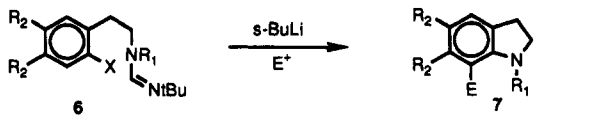


Table I. Indolines 7 from Phenethylformamidines, 6



entry	R_1	R_2	X	E^+	E	7, % yield[a]
a	Me	MeO	Cl	NH_4Cl	H	>99
b	*n*-Bu	MeO	Cl	NH_4Cl	H	93
c	*i*-Pr	MeO	Cl	NH_4Cl	H	95[c]
d	Me	H	Cl	NH_4Cl	H	40 (64)[b]
e	Me	H	Br	NH_4Cl	H	60
f	c-C_6H_{11}	MeO	Cl	NH_4Cl	H	94[d]
g	Me	MeO	Cl	MeI	Me	81
h	Me	MeO	Cl	D_2O	D	>98
i	Me	MeO	Cl	TMSCl	TMS	95
j	Me	MeO	Cl	$Br(CH_2)_2Br$	Br	83
k	Me	MeO	Cl	Cl_3CCCl_3	Cl	53

[a] Reactions performed using 2.0 equiv of *sec*-butyllithium in 0.02 M solutions of **6** in THF at −78 to −90 °C. The reactions were quenched immediately after addition of the *sec*-butyllithium. [b] Low yield due to warming of the solution to allow LiCl elimination which resulted in deprotonation of *N*-methyl group (R_1). When LDA was used as base, the yield increased to 64%. [c] The starting material **6** contained a second chloro substituent ortho to the phenethylamino group. Yield is for the 4-chloro-5,6-dimethoxyindoline. [d] This material slowly oxidized to the indole on standing for several days (HRMS).

(1) For some recently reported therapeutic uses of indolines see: (a) Siddiqui, M.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1523. (b) Somei, M.; Kawasaki, T. *Chem. Pharm. Bull.* **1989**, *37*, 3426.

(2) For a recent review of indoline chemistry see: Bird, C. W.; Cheeseman, G. W. H. In Katrizky, A. R.; Rees, C. W. *Comprehensive Heterocyclic Chemistry*; Pergamon: New York, 1984; Vol. 4, p 89.

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(5) (a) Mayer, J.; Cassady, J.; Nichols, D. *Heterocycles* **1990**, *31*, 1035. (b) Swenton, J.; Shih, C.; Chen, C.; Chou, C. *J. Org. Chem.* **1990**, *55*, 2019. (c) Watanabe, Y.; Huh, K.; Tsuji, Y. *J. Org. Chem.* **1990**, *55*, 581.

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(9) (a) Meyers, A. I.; Beard, R. *J. Org. Chem.* **1991**, *56*, 2091. (b) Highsmith, T.; Meyers, A. I. Asymmetric Synthesis of Alkaloids: The α-Alkylation of Nitrogen Heterocycles via Formamidine-Mediated Chiral Carbanions. *Advances in Heterocyclic Natural Product Synthesis*; JAI press: Greenwich, 1991.

(10) The N-substituted β-phenethylamine was prepared from the N-substituted amide of the corresponding phenylacetic acid, after chlorination. The overall yields ranged from 70 to 80%. Details may be found in the supplementary material.

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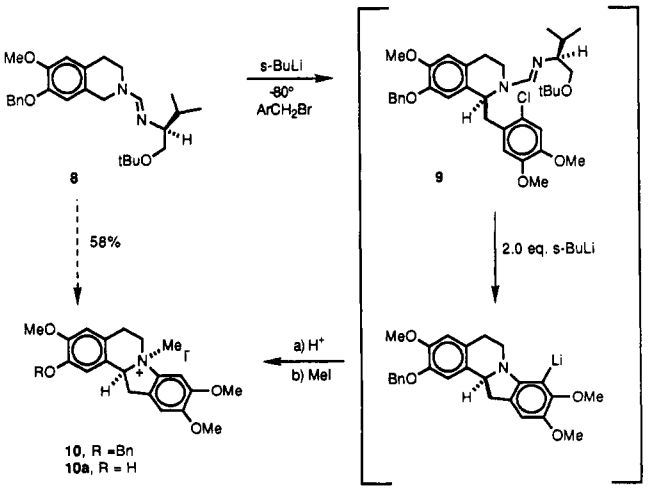
a similar fashion (MgX_2, CuX_2, ZnX_2, etc.) to allow a number of various organometallic intermediates to be accessed. In order to reach the indoline **3**, aqueous workup (or other electrophile introduction) furnished the 7-substituent and resulted in concomitant loss of the *tert*-butylamino moiety, detected as *t*-butylformamide by infrared spectroscopy, TLC, and NMR.

A series of phenethylformamidines **2** were examined using different electrophiles and varying the aromatic, nitrogen, and halogen substituents. These are tabulated in Table I. Although the reaction is most efficient with methoxy substituents due to facile ortholithiation, it also proceeded satisfactorily with unsubstituted *o*-halo phenethylamines. The drop in yield in the latter series appears mainly to be the result of slower benzyne formation, once the aromatic rings are lithiated. Elimination of LiCl to the benzyne is faster in the methoxy systems (<−78 °C) whereas the unsubstituted aromatics required temperatures above −50 °C to eject the LiCl.[11]

It is noteworthy that the indolines obtained via this route were all sensitive to facile aromatization to the corresponding indoles. Although this has been observed by others,[6] it constantly presented difficulty when we attempted to obtain combustion analyses. In order to minimize these autoxidations and decompositions, storage of the indolines in the freezer (−30 °C) under argon in sealed ampules allowed proper preservation of these materials.

As mentioned above, the *des*-methoxy aromatic formamidine **6d** required higher temperatures for benzyne formation which resulted in a lower yield (40%). These lower yields were caused by the higher temperatures opening the manifold to a number of side reactions by allowing for halogen–metal exchange, deprotonation of the methyl group, and addition of the base into the imine bond of the formamidine. We have managed to avoid these side reactions and increased the yield of indoline by simply using lithium diisopropylamide (LDA) as the base. Treatment of **6d** with 2.1 equiv of LDA at −78 °C in pentane and warming to rt gave, in a consistently clean reaction, the indoline **7d** in 64% yield (Table I, entry d).



Further examination of this efficient indoline process led us to the fact that cyclization of **6a** to **7a** can also be effected by 1.0 equiv of *sec*-butyllithium, if 1.0 equiv of LiBr was first introduced. This implies that lithium ion is first complexed to the formamidine prior to metalation, a fact observed several years ago.[12] Although only one example of the latter technique was performed, it is reasonable to assume that the other cases in Table I would behave in a similar fashion.

As a demonstration of the utility of this indoline synthesis, a formal asymmetric approach to the alkaloid (+)-cryptaustoline (**10a**)[13] was accomplished in a one-pot, highly efficient, manner and is described briefly below. Starting with the isoquinoline **8** equipped with the chiral formamidine,[14] metalation and alkylation with dimethoxychlorobenzyl bromide gave the isoquinoline **9**.

Without isolation, the synthesis of **10** was continued by simply adding 2.0 equiv of *sec*-butyllithium to the solution containing **9**. After 15 min, the reaction mixture was quenched with ammonium chloride followed immediately by addition of excess methyl iodide. In this fashion the alkaloid **10** precipitated (after several days) from solution in 58% overall yield from **8**. This material was identical in all respects to that prepared in a stepwise sequence earlier as well as the natural material (>94% ee).[13]

Further studies on this benzyne route to other heterocyclic systems are in progress.

Experimental Section

General. All proton and carbon NMR spectra were taken at 300 and 75 MHz, respectively. Melting points are uncorrected. Argon was used as the inert atmosphere and was passed through both a drying tube and an oxytrap (BASF catalyst) to remove moisture and oxygen. Tetrahydrofuran was distilled from sodium and benzophenone. Dichloromethane, hexanes, and triethylamine were distilled from calcium hydride.

Elemental analyses were performed by Desert-Analytics, Tuscon, AZ. High-resolution mass spectral analyses were kindly performed by Steve Klohr of Bristol-Myers Squibb Co.

General Procedure for the Synthesis of *N'-tert*-Butylformamidines 6a–f. In a typical procedure the appropriate amide[10] (5.85 g, 19.1 mmol) was weighed into a 100-mL round-bottomed flask equipped with a magnetic stirrer. The mixture was purged with argon and cooled in a 0 °C ice bath. Lithium aluminum hydride (1.45 g, 38.3 mmol) was slowly added and the reaction warmed to reflux for 24 h. The solution was cooled to rt and quenched using a Fieser quench (0.75 mL of H_2O, 1.5 mL of 10% NaOH, 3.0 mL of H_2O). The solids were filtered and the mixture concentrated. Due to the potential toxicity of these amines[15] they were taken on directly to the formamidines by warming with 1 equiv of *N,N*-dimethyl-*N'-tert*-butylformamidine[16] with a catalytic amount of ammonium sulfate. The system was set up with a flow of argon and a vent needle to allow for the liberation of dimethylamine. After 24 h the reaction was complete, and the formamidines **6** were purified by passing through a column (sg, 10% Et_3N, 30% EtOAc, 60% hexane) and isolated as viscous yellow oils. The spectral data of these compounds at rt revealed that rotational isomerism is present. Heating the NMR sample to 60 °C resulted in coalescence. The spectral data reported are those taken at rt. Combustion analyses were not attempted due to previous difficulties with acquiring satisfactory data. The hygroscopic, polar, and air sensitivity of formamidines preclude critical characterization in most cases.

***N*-Isopropyl-*N*-[(2,6-dichloro-4,5-dimethoxyphenyl)ethyl]-*N'-tert*-butylformamidine, 6c.** ^1H NMR: δ 7.39 (s, 1 H); 6.83 (s, 1 H); 3.84 (s, 3 H); 3.82 (s, 3 H); 3.90–3.78 (m, 1 H); 3.25–3.20 (m, 2 H); 3.12–3.07 (m, 2 H); 1.11 (s, 9 H); 1.05–1.03 (d, 6 H). ^{13}C NMR: δ 152.23; 149.12; 130.46; 130.11; 129.09; 112.37;

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(12) Meyers, A. I.; Fuentes, L.; Reiker, W. *J. Am. Chem. Soc.* **1983**, *105*, 2082.

(13) The asymmetric total synthesis of (+)-cryptaustoline via a lengthier synthesis and revision of its absolute stereochemistry has recently been the subject of another report from this laboratory: Meyers, A. I.; Sielecki, T. M. *J. Am. Chem. Soc.* **1991**, *113*, 2789.

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60.93; 56.55; 53.29; 49.52; 42.08; 31.98; 31.58; 30.17; 26.08; 21.53; 21.28. IR (thin film) cm^{-1}: 2964.7; 2360.2; 1643.5; 1589.5; 1479.7; 668.0.

***N*-Cyclohexyl-*N*-[(2-chloro-4,5-dimethoxyphenyl)ethyl]-*N'-tert*-butylformamidine, 6f.** ^1H NMR: δ 7.35 (s, 1 H); 6.82 (s, 1 H); 6.81 (s, 1 H); 3.84 (s, 3 H); 3.83 (s, 3 H); 3.85–3.83 (m, 1 H); 2.93–2.90 (m, 2 H); 2.93–2.88 (m 2 H); 1.77–1.28 (m, 10 H); 1.27 (s, 9 H). ^{13}C NMR: δ 148.23; 147.36; 129.91; 124.24; 113.66; 113.39; 112.28; 62.26; 59.49; 58.38; 55.76; 55.69; 55.56; 43.60; 41.38; 37.49; 33.28; 31.88; 25.99. IR (thin film) cm^{-1}: 2930.8; 1639.8; 1601.3; 1504.8; 1453.4; 1260.5; 1215.7; 1166.1. This compound shows several rotational isomers at rt. The rt spectra are included. The compound was also somewhat unstable to air and silica gel.

***N*-*n*-Butyl-*N*-[(2-chloro-4,5-dimethoxyphenyl)ethyl]-*N'-tert*-butylformamidine, 6b.** ^1H NMR: δ 7.17 (s, 1 H); 6.79 (s, 1 H); 6.70 (s, 1 H); 3.83 (s, 3 H); 3.82 (s, 3 H); 3.61–3.42 (t, 2 H); 3.11–3.01 (t, 2 H); 2.88–2.82 (m, 2 H); 1.50–1.41 (m, 2 H); 1.27–1.09 (m, 2 H); 1.09 (s, 9 H); 0.89–0.84 (t, 3 H). ^{13}C NMR: δ 149.88; (148.31; 148.09); 129.74; 125.01; 114.25; 113.87; 112.81; 56.45 (2 C); 53.08; 48.59; 47.35; 31.82; 31.56; 31.11; 20.25; 14.17. IR (thin film) cm^{-1}: 2959.3; 1643.8; 1605.9; 1511.9; 1463.9; 1386.0; 1355.9; 1216.9; 1166.2; 1046.9.

***N*-Methyl-*N*-[(2-bromophenyl)ethyl]-*N'-tert*-butylformamidine, 6e.** ^1H NMR: δ 7.33–7.30 (m, 1 H); 7.16–7.09 (m, 4 H); 3.40–3.36 (t, 2 H); 2.93–2.88 (t, 2 H); 2.82 (s, 3 H); 1.06 (s, 9 H). ^{13}C NMR: δ 150.16; 136.86; 133.95; 131.37; 129.49; 127.79; 126.85; 52.75; 51.13; 33.76; 32.54; 31.22. IR (thin film) cm^{-1}: 2963.2; 1645.8; 1474.5; 1442.5; 1212.5; 1074.4; 1052.5; 749.9.

***N*-Methyl-*N*-[(2-chloro-4,5-dimethoxyphenyl)ethyl]-*N'-tert*-butylformamidine, 6a.** ^1H NMR: δ 7.04 (s, 1 H); 6.79 (s, 1 H); 6.63 (s, 1 H); 3.79 (s, 3 H); 3.75 (s, 3 H); 3.40–3.35 (m, 2 H); 2.85–2.81 (m, 2 H); 2.83 (s, 3 H); 1.07 (s, 9 H). ^{13}C NMR: δ 162.42; 148.23; 147.84; 128.22; 124.55; 56.10; 53.17; 51.58; 49.35; 31.84; 30.85. IR (thin film) cm^{-1}: 2962.2; 1643.7; 1605.9; 1503.7; 1441.2; 1389.7; 1260.6; 1216.2; 1166.8; 1045.9.

General Procedure for the Synthesis of 7-Substituted Indolines 7. The appropriate formamidine, **6** (0.176 g, 0.50 mmol), was weighed into a 100-mL flame-dried round-bottomed flask equipped with a magnetic stirrer and kept under vacuum overnight to ensure dryness. Tetrahydrofuran (50 mL) was introduced, and the flask was cooled to −78 °C and purged thoroughly with argon. *sec*-Butyllithium (0.96 mL, 1.09 M, 1.04 mmol) was then added dropwise over 45 min. The solution immediately turned light yellow. The reaction was stirred for an additional 15 min at −78 °C to ensure completion and quenched with water, and the volatiles were removed. The residue was taken up in water and extracted three times into dichloromethane, and the combined organic phases were dried over K_2CO_3. Following concentration, the indolines were passed through a plug of silica gel using 5% Et_3N/10% EtOAc/85% hexane as the eluting solvent. The indolines were isolated as pale yellow oils unless otherwise specified.

***N*-Methylindoline, 7d.** The general procedure above was followed. The oxalate was made by adding oxalic acid to an ethanolic solution of the indoline and cooling (−10 °C) overnight. The oxalate was isolated as a faintly yellow solid: mp 100–102 °C (lit.[7] mp 103–104 °C).

Lithium Diisopropylamide Cyclization. Formamidine **6d** (0.26 g, 0.89 mmol) was weighed into a 100-mL flame-dried round-bottomed flask equipped with a magnetic stirrer and kept under vacuum overnight to ensure dryness. Pentane (50 mL) was introduced and the flask cooled to −78 °C and purged thoroughly with argon. Freshly prepared lithium diisopropylamide (1.86 mmol, 2.1 equiv) was added dropwise and the reaction left under argon to warm to rt overnight. The reaction mixture was quenched with water (2.0 mL), the volatiles were removed, and the residue was taken up in water and extracted three times with ethyl acetate. The combined organic phases were dried over K_2CO_3 and concentrated. Purification by passing through a plug of silica gel using 5% Et_3N/10% EtOAc/85% hexane as the eluting solvent gave, upon concentration, indoline **7d** in 64% yield. The material was identical to that prepared using the general procedure above.

***N*-Methyl-5,6-dimethoxyindoline, 7a.** ^1H NMR: δ 6.74 (s, 1 H); 6.18 (s, 1 H); 3.85 (s, 3 H); 3.79 (s, 3 H); 3.25–3.19 (t, 2 H); 2.87–2.81 (t, 2 H); 2.70 (s, 3 H) (lit.[6] proton data identical).

Lithium Bromide Cyclization. Lithium bromide was dried for 2 days under vacuum at 100 °C. Formamidine **6a** (0.29 g, 0.94 mmol) was weighed into a three-necked 100-mL round-bottomed flask equipped with a magnetic stirrer and kept under vacuum overnight to ensure dryness. Lithium bromide (0.09 g, 1.0 mmol) was introduced via a dry addition funnel followed by tetrahydrofuran (40 mL). The reaction was stirred under argon at rt for 30 min. Cooling to −78 °C in a dry ice/acetone bath was followed by the dropwise addition of *sec*-butyllithium (0.80 mL, 1.28 M). After 10 min the solution was quenched with water (2 mL) and worked up following the procedure above. The indoline **7a** was isolated in 96% yield and was identical to the material prepared using the above general procedure.

***N*-Methyl-5,6-dimethoxy-7-deuterioindoline, 7h.** The above general procedure was used, followed by quenching with D_2O. ^1H NMR: δ 6.74 (s, 1 H); 3.85 (s, 3 H); 3.79 (s, 3 H); 3.25–3.19 (t, 2 H); 2.88–2.83 (t, 2 H); 2.71 (s, 3 H). The material was identical in every respect to the protio compound except for the absence of the proton at 6.18 ppm.

***N*-Cyclohexyl-5,6-dimethoxyindoline, 7f.** ^1H NMR: δ 6.70 (s, 1 H); 6.09 (s, 1 H); 3.83 (s, 3 H); 3.77 (s, 3 H); 3.33–3.27 (t, 2 H); 3.27–3.21 (m, 1 H); 2.86–2.81 (t, 2 H); 1.83–1.80 (m, 4 H); 1.36–1.30 (m, 6 H). ^{13}C NMR: δ 149.14; 145.85; 141.08; 120.98; 111.04; 94.36; 57.35; 56.50; 55.35; 47.29; 28.63; 28.31; 26.42; 26.13; 26.05. IR (thin film) cm^{-1}: 2928; 2852; 1613; 1501; 1451; 1227; 1204; 1101. The compound air oxidized to the indole on standing. HRMS: calcd for $C_{16}H_{21}NO_2$ 259.1572, found 259.1566.

***N*-Butyl-5,6-dimethoxyindoline, 7b.** ^1H NMR: δ 6.72 (s, 1 H); 6.16 (s, 1 H); 3.83 (s, 3 H); 3.78 (s, 3 H); 3.24–3.22 (t, 2 H); 2.98–2.93 (t, 2 H); 2.88–2.83 (t, 2 H); 1.59–1.52 (m, 2 H); 1.42–1.37 (m, 2 H); 0.98–0.93 (t, 3 H). ^{13}C NMR: δ 149.07; 147.53; 141.55; 120.77; 110.79; 94.24; 57.29; 56.28; 53.99; 50.28; 29.75; 28.48; 20.44; 13.98. IR (thin film) cm^{-1}: 2955; 2931; 2862; 1615; 1503; 1463; 1227; 1203; 1188; 1090; 1026. HRMS: calcd for $C_{14}H_{21}NO_2$ 235.1573, found 235.1581.

***N*-Isopropyl-4-chloro-5,6-dimethoxyindoline, 7c.** ^1H NMR: δ 6.33 (s, 1 H); 4.18 (s, 3 H); 4.10 (s, 3 H); 3.84–3.72 (m, 1 H); 3.74–3.67 (t, 2 H); 3.30–3.24 (t, 2 H); 1.54–1.50 (d, 6 H). ^{13}C NMR: δ 153.73; 148.26; 136.83; 125.23; 120.41; 92.35; 61.31; 56.86; 46.54; 45.60; 27.52; 18.46. IR (thin film) cm^{-1}: 2967.1; 2933.1; 1613.5; 1489.8; 1456.5; 1413.2; 1322.4; 1237.8; 1041.2; 1022.2. HRMS: calcd for $C_{13}H_{18}ClNO_2$ 255.1026, found 255.1020.

***N*-Methyl-5,6-dimethoxy-7-methylindoline, 7g.** The general procedure was used using 1.5 equiv of methyl iodide as the quench. The mixture was then allowed to warm to rt overnight and worked up as previously described. ^1H NMR: δ 6.61 (s, 1 H); 3.74 (s, 3 H); 3.73 (s, 3 H); 2.90–2.86 (t, 2 H); 2.83–2.80 (t, 2 H); 2.81 (s, 3 H); 2.25 (s, 3 H). ^{13}C NMR: δ 146.99; 126.24; 116.99; 107.39; 92.14; 60.39; 57.95; 56.54; 41.67; 29.33; 11.48. IR (thin film) cm^{-1}: 2951; 1611; 1480; 1465; 1409; 1253; 1223; 1062; 946. HRMS calcd for $C_{12}H_{17}NO_2$ 207.1260, found 207.1255.

***N*-Methyl-5,6-dimethoxy-7-chloroindoline, 7k.** The general procedure was used quenching with 1.5 equiv of hexachloroethane in 5 mL of THF. The mixture was then allowed to warm to rt overnight and worked up as previously described. ^1H NMR: δ 6.65 (s, 1 H); 3.80 (s, 3 H); 3.77 (s, 3 H); 3.33–3.28 (t, 2 H); 3.00 (s, 3 H); 2.91–2.88 (t, 2 H). ^{13}C NMR: δ 146.84; 145.33; 143.84; 127.52; 112.58; 109.14; 60.66; 57.91; 57.15; 40.02; 29.19. IR (thin film) cm^{-1}: 2936; 2839; 1615; 1570; 1482; 1466; 1416; 1248. HRMS: calcd for $C_{11}H_{14}ClNO_2$ 227.0713, found 227.0707.

***N*-Methyl-5,6-dimethoxy-7-bromoindoline, 7j.** The general procedure was used quenching with 1.5 equiv of dibromoethane. The mixture was then allowed to warm to rt overnight and worked up as previously described. ^1H NMR: δ 6.69 (s, 1 H); 3.79 (s, 3 H); 3.78 (s, 3 H); 3.36–3.31 (t, 2 H); 3.01 (s, 3 H); 2.94–2.88 (t, 2 H). ^{13}C NMR: δ 147.26; 146.46; 145.3; 128.51; 110.22; 102.55; 60.86; 58.25; 57.49; 40.96; 29.43. IR (thin film) cm^{-1}: 2933; 2849; 1562; 1480; 1465; 1414; 1245; 1071; 1036. HRMS: calcd for $C_{11}H_{14}BrNO_2$ 271.0208, found 271.0201.

***N*-Methyl-5,6-dimethoxy-7-(trimethylsilyl)indoline, 7i.** The general procedure was used quenching with 1.5 equiv of trimethyl silyl chloride. The mixture was then allowed to warm to rt overnight and worked up as previously described. ^1H NMR: δ 6.79 (s, 1 H); 3.78 (s, 3 H); 3.72 (s, 3 H); 3.29–3.24 (t, 2 H); 2.94–2.91 (t, 2 H); 2.65 (s, 3 H); 0.35 (s, 9 H). ^{13}C NMR: δ 154.74; 154.06; 146.79; 127.56; 118.64; 111.18; 60.90; 56.77; 56.25; 46.76; 28.90; 1.46. IR (thin film) cm^{-1}: 3001; 1644; 1510; 1432; 1210; 1060. HRMS: calcd for $C_{14}H_{23}NO_2Si$ 265.1498, found 265.1505.

O-Benzylcryptaustoline, 10. 7-(Benzyloxy)-6-methoxyisoquinoline with the formamidine 8 (0.12g, 0.26 mmol) in place[14] was introduced into a 100-mL flame-dried round-bottomed flask equipped with a magnetic stirrer. Tetrahydrofuran (50 mL) was added and the mixture cooled to −78 °C. The system was purged with argon following which *sec*-butyllithium (0.23 mL, 1.28 M, 0.29 mmol) was added dropwise over 15 min. The dark red solution was stirred an additional 20 min, and 2-chloro-4,5-dimethoxybenzyl bromide[13] (0.084 g, 0.32 mmol) in 5 mL of tetrahydrofuran was rapidly injected. The solution immediately turned clear, and after 10 min of additional stirring an additional 2 equiv of *sec*-butyllithium (0.46 mL, 1.28 M, 0.58 mmol) was added dropwise to the solution. Following 10 min of stirring, 1 equiv of NH_4Cl was added and the mixture warmed to rt. An aliquot of the cyclized amine was isolated for spectral evaluation and gave the following: mp 131–133 °C dec. ^1H NMR ($CDCl_3$): δ 7.39 (s, 1 H); 6.69 (s, 2 H); 6.50 (s, 2 H); 6.30 (s, 1 H); 5.12 (s, 2 H); 4.81–4.69 (1 H, q); 3.84 (s, 3 H); 3.78 (s, 3 H); 3.73 (s, 3 H); 3.60–2.80 (m, 6 H). ^{13}C NMR: δ 148.23; 148.18; 147.64; 146.14; 137.32; 130.64; 128.83; 128.48; 128.02; 127.75; 127.36; 127.23; 114.17; 112.91; 112.70; 112.28; 71.42; 56.15; 56.12; 55.97; 55.24; 40.49; 40.21; 29.51. IR cm^{-1}: 2931; 1606; 1508; 1219; 861. To complete the synthesis, excess methyl iodide (1.056 mmol, 4 equiv) was added and the flask placed in the freezer (−20 °C) for 1 week. The product, **10**, was collected as an off-white solid in 58% yield, mp 231–233 °C dec (lit.[17] mp 224–226 °C dec). $[\alpha]_D$: +48.5° (*c* 1.0, acetone), compared to material form another route[13] $[\alpha]_D$ +47.8° (*c* 0.8, acetone). The material was debenzylated following the procedure of Kametani and Ogasawara[17] to give the alkaloid $[\alpha]_D$ +141° (*c* 0.6, ethanol); natural material $[\alpha]_D$ −150° (*c* 0.4, ethanol).[17] The optical rotation indicated that the synthetic material had an ee of 94%.

Acknowledgment. The authors are grateful to the National Science Foundation and Bristol-Myers Squibb for support of our program and to Dr. Steve Klohr of Bristol-Meyers Squibb for the HRMS spectra. We would also like to thank Mr. Richard Hutchings for his technical assistance.

Supplementary Material Available: Experimental details and physical properties of the precursors to **6** and a ^1H or ^{13}C NMR spectrum of each indoline compound (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Preparation of Pyrrolo[2,1-*b*][1,3]benzothiazin-9-ones via Intramolecular Sulfenylation of an *N*-Acylpyrrole[1]

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Received January 28, 1992

Pyrrolo[2,1-*b*][1,3]benzothiazin-9-one (**6a**) was synthesized in 45% overall yield from thiosalicylic acid in six steps. The title compound (88%) and its 1-trifluoroacetyl (83%) and 1-formyl derivatives were synthesized via intramolecular reaction of 1-(2-ethylsulfinyl)benzoylpyrrole (**5**) by thermal cyclization or treatment with trifluoroacetic anhydride or DMF/$POCl_3$, respectively. The key step in each case is formation of the heterocycle by sulfoxide activation followed by C–S bond formation via attack *at sulfur*. Reaction of **6a** with common electrophiles (trifluoroacetic anhydride (86%), $POCl_3$/DMF (75%), and acetyl nitrate) indicates that C-1 is the predominant site of electrophilic substitution.

Introduction

The reaction of indole and pyrrole with electrophilic sulfur species to form C–S bonds is well-documented. Alkylthio[2] groups have been introduced into these systems using the original Swern reagent (prepared from DMSO/trifluoroacetic anhydride[3]) and the original Corey–Kim reagent (prepared from *N*-chlorosuccinimide/dimethyl sulfide[4]) or related reagents.[5] Arenesulfenyl iodides, formed in situ from aromatic thiols and KI/I_2, react with pyrroles (highly substituted to avoid ring iodination) to give pyrrolyl aryl sulfides.[6] For example, methyl 2-mercaptobenzoate in the presence of 2,4-dimethyl-3-pyrrolecarboxylic acid ethyl ester gave the precursor to the only reported pyrrolo[2,1-*b*][1,3]benzothiazin-9-one derivative (1).[6]

Intramolecular capture of electrophilic sulfur species has been exploited in the synthesis of fused heteroaromatic systems. Oxidative cyclization of arylthioureas to 2-aminobenzothiazoles has been accomplished by sulfur activation via treatment with bromine[7,8] or inorganic halides (thionyl chloride;[9] sulfuryl chloride[10]). This methodology has been extended to substituted 3-thienylthioureas and pyrazolylthioureas to afford thienyl[3,2-*d*]thiazoles[11a] and pyrazolo[3,4-*d*]thiazoles,[11b] respectively. In addition, *N*-arylbenzamidines can be converted to 1,2,4-benzothiadiazines upon treatment with *N*-chlorosuccinimide and 4,4′-thiobis(morpholine).[12]

A major problem in using positive halogen species to activate thiols or sulfides for intramolecular sulfenylation

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