ALDOL CONDENSATION OF *N*-ALKYLATED-3-ARYL-4,6-DIMETHOXY-7-FORMYLINDOLES AS A GOOD METHOD FOR THE SYNTHESIS OF 1-ARYL-6,8-DIMETHOXYPYRROLO[3,2,1-*hi*]INDOLE-4-CARBOXYLATES

Jumina *

Department of Chemistry, Faculty of Mathematics and Natural Sciences, Gadjah Mada University, Sekip Utara Bulaksumur Yogyakarta Indonesia 55281

Received 10 May 2006; Accepted 6 June 2006

ABSTRACT

*Alkylation of 3-aryl-4,6-dimethoxyindole **3a** and **3b** with methyl and ethyl α-bromoacetates afforded good yields of indol-1-ylacetates **4**. Treatment of these indoles **4** with the Vilsmeier formylation reagent gave formylindoles **5** in 54-81 % yield. These formylindole **5** underwent intramolecular aldol condensation when treated with sodium hydride in tetrahydrofuran to give pyrroloindole-4-carboxylates **6** in 30-60 % yield. Structural assignment based on spectroscopic data confirmed the structure of the synthesized pyrroloindoles. In the case of pyrroloindole **6c**, the structure of this molecule was also proven by X-ray crystallography data.*

Keywords: *indole, pyrroloindole, aldol condensation, alkylation, and formylation*.

INTRODUCTION

Pyrrolo[3,2,1-*hi*]indoles **1** are indole molecules bearing **2** a linking etheno group between N1 and C7. This class of compounds is synthetically interesting as these would be the benzo-analogues of the important pyrrolizidine skeleton present in numerous biologically-active alkaloids [1,2]. Some limited examples of pyrrolo[3,2,1-*hi*]indoles have been reported in the literature, but only a few synthetic routes towards these molecules have been investigated.

The first example of a pyrrolo[3,2,1-*hi*]indole was synthesized by Anet and coworkers [3] in 1961. The strategy included a simple oxidation of a dihydro-pyrroloindole formed by a Fischer synthesis [4-6] on an *N*-aminoindoline. The pyrroloindole was obtained in 20% yield and its elemental analysis was in agreement with the proposed structure. The ^{1}H n.m.r. spectrum showed the presense of three aromatic protons appearing as seven lines of an AB_2 system and four methyl groups which show up as two singlets of equal intensity.

A similar strategy was employed by Paudler and Shin [7] in 1969 who successfully constructed the parent pyrrolo[3,2,1-*hi*]indole **1** from the corresponding *N*-aminoindoline. Investigation using n.m.r. showed that all protons in the the parent pyrroloindole **1** appeared in more deshielded regions than those of the dihydro derivative. Moreover, the ^{1}H n.m.r. spectrum also proved that pyrroloindole **1** is planar as H1 and H5 were identical (6.60 ppm), as well as H2 and H4 (2.88 ppm), also H6 and H8 (2.47 ppm). It was also noted that the ultraviolet spectrum of pyrroloindole **1** was insensitive to acids, and indicated a clearly enhanced conjugation in comparison to that of the dihydro derivative. Therefore, it was concluded that pyrroloindole **1** is an aromatic, nonbasic and planar hetero aromatic compound.

The method for the synthesis of pyrroloindoles developed by Paudler and Shin seems to be straightforward as the reactions gave almost quantitative yields in every stage. However, application of this Fischer strategy to construct methoxy-substituted pyrroloindoles might encounter difficulties. It is known that arylhydrazines bearing strong electron donating groups, especially when oriented *ortho*- or *para*- to the hydrazine unit, gave low yields [8] or failed [9] to give the desired indole or its precursor under the standard Fischer synthesis.

The reaction of *N,N*-diphenacylaniline with polyphosphoric acid (PPA) has been reported by Bartsch [10,11] to afford either 1-phenacyl-3-phenylindole or 1,5-diphenylpyrrolo[3,2,1-*hi*]indole. When the reaction was carried out at 130^{o}C for 4 hours, 1-phenacyl-3-phenylindole was the main product. However, when the reaction was performed at the same temperature but in a much longer period of time (50 hours), 1,5-diphenylpyrrolo[3,2,1-*hi*]indole was obtained in 39%. An attempt to develop the Bartsch method has been conducted by Keller [12] who reacted *N,N*-di(4'-bromophenacyl)-3,5-dimethoxyaniline with PPA under the same conditions as reported by Bartsch. However, instead of the symmetrical pyrroloindole, the main outcome of this reaction was 3-bromo-5-(4'-bromophenyl)-9,11-dimethoxydibenz[*b,g*]indolizine.

Here the author reports the synthesis of 6,8-dimethoxy-1-arylpyrroloindole-4-carboxylates **6** from 4,6-dimethoxy-3-arylindoles **5** through the aldol condensation of the related N-alkylated 3-aryl-4,6-dimethoxyindoles. Apart from spectroscopic data, the structure of the synthesized pyrroloindole was also proven on the basis of X-ray crystal structure.

* Corresponding author. Phone / fax : 0062-274-545188
Email address : pak_jumina@yahoo.com

EXPERIMENTAL SECTION

General information

Melting points were measured on a Reichert microscope melting point apparatus and were uncorrected. Microanalyses were performed by Dr. H.P. Pham of the University of New South Wales. ^{1}H n.m.r. and ^{13}C n.m.r. spectra were recorded in the designated solvents on a Bruker AC300F (300 MHz) or a Bruker AM500 (500MHz) spectrometer. Chemical shifts were determined on the δ scale internally referenced to the solvent peaks: $CDCl_3$ (7.30 ppm, 77.7 ppm) and DMSO-d_6 (2.50 ppm, 39.9 ppm). Ultraviolet spectra were measured on a Hitachi U-3200 spectrometer and refer to solutions in absolute methanol. Infrared spectra were obtained on a Perkin Elmer 298 IR spectrometer and refer to paraffin mulls. The E.I. mass spectra were recorded on a VG Quattro mass spectrometer at 70eV ionisation voltage and 200°C ion source temperature by Dr. Joe Brophy. E.S. mass spectra were recorded on a VG Quattro mass spectrometer at 4000 volts probe voltage, 1000 volts counter electrode, 65 volts cone voltage using a mixture of acetonitrile and water (1:1) containing 1% acetic acid as the solvent and at 5μL/min flow rate also by Dr. Joe Brophy. X-ray crystal structure determination was performed by Mr. Don Craig of the University of New South Wales.

Flash column chromatography was carried out using Merck 230-400 mesh silica gel and refers to the technique described by Still [13] using pressure at the top of the column. Suction chromatography was performed using Merck 60H silica gel and refers to the technique of applying suction at the base of the column. Preparative thin layer chromatography was carried out on 20x20x0.1 cm plates using Merck silica gel 7730 $60GF_{254}$. Compounds were detected by short and long wavelength ultraviolet light.

4,6-Dimethoxy-3-phenylindole **3a** and 3-(4'-bromophenyl)-4,6-dimethoxyindole **3b** were prepared according the method as reported by Black and co-workers [14].

Methyl 4,6-dimethoxy-3-phenylindol-1-ylacetate (4a)

A mixture of powdered potassium hydroxide (0.16 g, 2.8 mmol) and dimethyl sulfoxide (10 mL) was stirred at room temperature for 10 minutes, then phenylindole **3a** (0.5 g, 2.0 mmol) was added, and the mixture stirred for another 30min. Methyl α-bromoacetate (0.4 mL, 4.3 mmol) was added dropwise, and the stirring continued overnight. The resulting brown-yellow mixture was diluted with water (70 mL), extracted with dichloromethane (3x60 mL), and the combined organic layers were washed with water, dried over magnesium sulfate and evaporated to give a brown oil. Flash chromatography and elution with dichloromethane gave the methyl indolylacetate as a white solid (0.47 g, 72 %), m.p. 103-105°C. (Found: C, 70.5; H, 6.2; N, 4.4. $C_{19}H_{19}NO_4$ requires C, 70.1; H, 5.9; N, 4.3 %). λ_{max} 208 nm (ε 23200), 224 (27640), 269 (10800), 279 (11280). ν_{max} 1750, 1580, 1270, 1210, 1200, 1160, 1040, 770, 700 cm^{-1}. ^{1}H n.m.r. ($CDCl_3$): δ 3.64, 3.69, 3.76, each s, OMe; 4.64, s, CH_2; 6.19, d, *J* 2.0 Hz, H5; 6.22, d, *J* 2.0 Hz, H7; 6.79, s, H2; 7.16, t, *J* 7.1 Hz, H4'; 7.26, t, *J* 7.1 Hz, H3'; 7.53, d, *J* 7.1 Hz, H2'. ^{13}C n.m.r. ($CDCl_3$): δ 47.9, CH_2; 52.6, 55.2 and 55.7, OMe; 85.1, C5; 92.3, C7; 124.8, C2; 110.9, 118.9, 135.7, 139.0, 155.2 and 157.9, ArC; 125.7, 127.5 and 129.5, ArCH; 168.9, CO. Mass spectrum: *m/z* 326(M+1, 20%), 325(M, 100), 310(20), 266(48), 250(29), 237(18), 208(21), 180 (18), 152(25), 134(36), 105(56), 83(20), 77(34), 69(46), 57(47).

Methyl 3(4'-bromophenyl)-4,6-dimethoxyindol-1-yl acetate (4b)

This was prepared by reacting a suspension of potassium hydroxide (0.35 g, 6.33 mmol) in dimethylsulfoxide (25 mL) with bromophenylindole **3b** (1.50 g, 4.52 mmol) and methyl α-bromoacetate (1.1 mL, 11.30 mmol) according to the method of preparation of compound **4a**. The resulting brown solid was flash chromatographed, and elution with light petroleum in dichloromethane (3:7) gave the methyl indolylacetate as a yellow-reddish solid (1.28 g, 70 %), m.p. 123-125°C. (Found: C, 56.5; H, 4.5; N, 3.4. $C_{19}H_{18}BrNO_4$ requires C, 56.5; H, 4.5; N, 3.5 %). λ_{max} 210 nm (ε 19300), 230 (19500), 280 (10600), 298 (9300). ν_{max} 1740, 1620, 1590, 1330, 1280, 1210, 1170, 1140, 1010 cm^{-1}. ^{1}H n.m.r. ($CDCl_3$): δ 3.77, 3.80 and 3.87, each s, OMe; 4.77, s, CH_2; 6.30, s, H5; 6.32, s, H7; 6.89, s, H2; 7.47, s, ArH. ^{13}C n.m.r. ($CDCl_3$): δ 47.9, CH_2; 52.6, 55.1 and 55.7, OMe; 85.1, C5; 92.4, C7; 110.6, 117.7, 119.7, 134.7, 139.0, 155.0 and 158.0, ArC; 124.8, C2; 130.6 and 131.1, ArCH; 168.8, CO. Mass spectrum: *m/z* 406(M+1, ^{81}Br, 20%), 405(M, ^{81}Br, 97), 404(M+1, ^{79}Br, 20), 403(M, ^{79}Br, 100), 346(33), 344(31), 309(45), 207(30), 174(30), 152(28), 69(40), 59(29), 43(35).

Ethyl 3(4'-bromophenyl)-4,6-dimethoxyindol-1-yl-acetate (4c)

A suspension of powdered potassium hydroxide (0.12 g, 2.11 mmol) in dimethylsulfoxide (10 mL) was reacted with indole **3b** (0.50 g, 1.51 mmol) followed by ethyl α-bromoacetate (0.4 mL, 3.59 mmol) according to

the method of preparation of compound **4a**. The resulting brown oil was flash chromatographed, and elution with dichloromethane afforded the ethyl indolylacetate as an off-white solid (0.63 g, 78 %), m.p. 104-105°C. (Found: C, 57.1; H, 4.6; N, 3.1; $C_{20}H_{20}BrNO_4$ requires C, 57.4; H, 4.8; N, 3.4 %). λ_{max} 208 nm (ε 29800), 223 (31000), 231 (25400), 284 (13500), 299 (12100). ν_{max} 1740, 1620, 1280, 1220, 1200, 1160, 790 cm^{-1}. ^1H n.m.r. ($CDCl_3$): δ 1.28, t, *J* 7.1 Hz, $CH_2\underline{C}H_3$; 3.80 and 3.86, each s, OMe; 4.24, q, *J* 7.1 Hz, $\underline{C}H_2CH_3$; 4.76, s, CH_2; 6.28, d, *J* 2.0 Hz, H5; 6.31, d, *J* 2.0 Hz, H7; 6.91, s, H2; 7.47, s, ArH. ^{13}C n.m.r. ($CDCl_3$): δ 14.2, $CH_2\underline{C}H_3$; 48.1, CH_2; 55.2 and 55.7, OMe; 61.8, $\underline{C}H_2CH_3$; 85.2, C5; 92.5, C7; 124.9, C2; 110.7, 117.7, 119.7, 134.8, 139.0, 155.0 and 158.0, ArC; 130.6 and 131.1, ArCH; 168.3, $\underline{C}O_2Et$. Mass spectrum: *m/z* 419(M, ^{81}Br, 13%), 417(M, ^{79}Br, 15), 286(13), 185(93), 183(100), 157(29), 155(31), 76(37), 75(32), 69(39), 57(41), 55(36).

Ethyl 4,6-dimethoxy-7-formyl-3-phenylindol-1-yl-acetate (5a)

Indole **3a** (0.66 g, 2.61 mmol) was reacted with a suspension of powdered potassium hydroxide (0.21g, 3.65 mmol) in dimethylsulfoxide (12 mL) followed by ethyl α-bromoacetate (0.7 mL, 6. 53 mmol) according to the method of preparation of compound **4a**. The resulting brown oil (0.67 g) was dissolved in dry dimethylformamide (4 mL), cooled in ice, then a cooled solution of phosphoryl chloride (0.3 mL, 2.94 mmol) in dry dimethylformamide (1.0 mL) was added dropwise. The mixture was stirred at 0° for 1 hour, then at room temperature for another 30 minutes. Cold water (10 mL) was added followed by excess 2 N sodium hydroxide solution until the mixture was strongly basic. The suspension was stirred at room temperature overnight, the resulting precipitate was filtered, washed with water and dried. Flash chromatography and elution with dichloromethane afforded the ethyl formylindole as a brown solid (0.52 g, 54 %), m.p. 135-137°C. (Found: C, 68.5; H, 5.8; N, 3.6. $C_{21}H_{21}NO_5$ requires C, 68.7; H, 5.8; N, 3.8 %). λ_{max} 216nm (ε 9900), 233 (9900), 262 (11000), 337 (7200). ν_{max} 1755, 1650, 1590, 1570, 1555, 1280, 1225, 1210 cm^{-1}. ^1H n.m.r. ($CDCl_3$): δ 1.29, t, *J* 8.2 Hz, $CH_2\underline{C}H_3$; 3.82 and 3.93, each s, OMe; 4.22, q, *J* 8.2 Hz, $\underline{C}H_2CH_3$; 5.33, s, CH_2; 6.21, s, H5; 6.80, s, 2; 7.31, m, H2',3'; 7.51, d, *J* 9.1 Hz, H4'; 10.39, s, CHO. ^{13}C n.m.r. ($CDCl_3$): δ 14.1, $CH_2\underline{C}H_3$; 53.1, CH_2; 55.1 and 56.8, OMe; 61.1, $\underline{C}H_2CH_3$; 87.7, C5; 106.6, 112.9, 119.1, 135.1, 136.5, 160.9 and 164.9, ArC; 126.0, 127.4, 129.1 and 129.7, ArCH; 169.5, CO; 188.1 CHO. Mass spectrum: *m/z* 368(M+1, 18%), 367(M, 100), 338(13), 310(22), 294(57), 266(16), 236(27), 152(13), 139(14), 81(13), 69(22).

Methyl 3-(4'-bromophenyl)-7-formyl-4,6-dimethoxy-indol-1-ylacetate (5b)

Indole **4b** (0.65 g, 1.61 mmol) in dry dimethylformamide (3.5 mL) was reacted with phosphoryl chloride (0.25 mL, 2.41 mmol) in dry dimethylformamide (1.0 mL) according to the method of preparation of compound **5a**. The resulting solid was flash chromatographed, and elution with dichloromethane/chloroform (1:1) yielded the methyl formylindole as a brown solid (0.51g, 73 %), m.p. 243-245°C. (Found: C, 55.3; H, 4.3; N, 3.1. $C_{20}H_{18}BrNO_5$ requires C, 55.6; H, 4.2; N, 3.2 %). λ_{max} 212 nm (ε 18400), 227 (17200), 257 (10300), 281 (5800). ν_{max} 1770, 1600, 1590, 1570, 1280, 1225 cm^{-1}. ^1H n.m.r. (DMSO-d_6): δ 3.63, 3.90 and 3.98, each s, OMe; 5.33, s, CH_2; 6.54, s, H5; 7.24, s, H2; 7.38 and 7.53, 2d, *J* 7.8 Hz, ArH; 10.23, s, CHO. ^{13}C n.m.r. (DMSO-d_6): δ 52.0, 55.8 and 57.3, OMe; 52.4, CH_2; 88.9, C5; 130.2, 130.5 and 131.3, ArCH; 106.0, 111.8, 116.4, 119.3, 134.4, 135.9, 160.5 and 164.5, ArC; 169.8, CO; 187.1, CHO. Mass spectrum: *m/z* 433(M, ^{81}Br, 14%), 432(M+1, ^{79}Br, 12), 431(M, ^{79}Br, 28), 361(100), 359(95), 265(53), 194(23), 178(27), 150(36), 139(38), 83(48), 69(28), 59(22).

Ethyl 3-(4'-bromophenyl)-7-formyl-4,6-dimethoxy indol-1-ylacetate (5c)

This was prepared by reacting indole **4c** (0.60 g, 1.50 mmol) in dry dimethylformamide (4.0 mL) with phosphoryl chloride (0.20 mL, 2.25 mmol) in dry dimethylformamide (1.0 mL) according to the method of preparation of compound **5a**. The resulting solid was flash chromatographed, and elution with dichloromethane gave the formylindole as a white solid (0.54 g, 81 %), m.p. 209-211°C. (Found: C, 56.5; H, 4.5; N, 3.0; $C_{21}H_{20}BrNO_5$ requires C, 56.5; H, 4.5; N, 3.1 %). λ_{max} 208 nm (ε 10700), 234 (8700), 259 (11200), 333 (4100). ν_{max} 1750, 1650, 1580, 1550, 1270, 1210, 810, 780 cm^{-1}. ^1H n.m.r. ($CDCl_3$): δ 1.28, t, *J* 7.1 Hz, $CH_2\underline{C}H_3$; 3.86 and 3.96, each s, OMe; 4.22, q, *J* 7.1 Hz, $\underline{C}H_2CH_3$; 5.33, s, CH_2; 6.24, s, H5; 6.79, s, H2; 7.35 and 7.46, 2d, *J* 8.5 Hz, ArH; 10.71, s, CHO. ^{13}C n.m.r. ($CDCl_3$): δ 14.2, $CH_2\underline{C}H_3$; 53.2, CH_2; 55.3 and 57.0, OMe; 61.3, $\underline{C}H_2CH_3$; 87.9, C5; 129.1, C2; 106.9, 118.0, 120.2, 134.2, 136.7, 160.8, 165.1 and 169.5, ArC; 130.5 and 131.4, ArCH; 188.2, CO;

213.8, CHO. Mass spectrum: *m/z* 448(M+1, ^{81}Br, 10%), 447(M, ^{81}Br, 62), 446(M+1, ^{79}Br, 10), 445(M, ^{79}Br, 67), 374(45), 372(49), 346(18), 344(27), 220(28), 207(33), 192(33), 178(32), 163(36), 151(39), 69(69), 55(100), 54(100).

Ethyl 6,8-dimethoxy-1-phenylpyrrolo[3,2,1-hi]indole-4-carboxylate (6a)

Sodium hydride (80 % in paraffin oil, 0.25 g, 8.33 mmol) was added into an ice-cooled solution of formylindole **5a** (1.50 g, 4.20 mmol) in dry tetrahydrofuran (100 mL). The mixture was heated at reflux for 2 hours, then allowed to cool and excess sodium hydride was destroyed by treatment with ice-water (120 mL) cautiously. The resulting suspension was extracted with dichloromethane (3x90 mL), and the combined organic layers were washed with water, dried over magnesium sulfate and evaporated to give a brown solid. Flash chromatography and elution with light petroleum in dichloromethane (1:9) gave the pyrroloindole as a yellow solid (0.88 g, 60 %), m.p. 148-151°C. (Found: C, 71.9; H, 5.6; N, 3.9. $C_{21}H_{19}NO_4$ requires C, 72.2; H, 5.5; N, 4.0 %). λ_{max} 212 nm (ε 58000), 236 (45500), 265 (24000), 333 (52500). ν_{max} 1700, 1595, 1230, 1200, 1180 cm^{-1}. ^{1}H n.m.r. ($CDCl_3$): δ 1.41, t, *J* 7.1 Hz, $CH_2\underline{C}H_3$; 3.93 and 4.16, each s, OMe; 4.41, q, *J* 7.1 Hz, $C\underline{H}_2CH_3$; 6.41, s, H7; 7.25, t, *J* 7.7 Hz, H4'; 7.38, t, *J* 7.7 Hz, H3'; 7.52, s, H5; 7.83, s, H2; 7.84, t, *J* 7.7 Hz, H2'. ^{13}C n.m.r. ($CDCl_3$): δ 14.5, $CH_2\underline{C}H_3$; 56.3 and 57.9, OMe; 61.0, $\underline{C}H_2CH_3$; 93.50, 103.62, 104.04, 122.44, 126.82, 127.40, 134.25 and 158.05, ArC; 95.6, C7; 115.9, C5; 119.2, C2; 126.7, 128.0 and 128.4, ArCH. Mass spectrum: *m/z* 350(M+1, 22%), 349(M, 100), 335(13), 321(27), 262(15), 190(29), 163(29), 77(13), 69(28).

Methyl 1-(4'-bromophenyl)-6,8-dimethoxypyrrolo-[3,2,1-hi]indole-4-carboxylate (6b)

This was prepared by reacting sodium hydride (80 % in paraffin oil, 14 mg, 0.47 mmol) with a solution of the formylindole **5b** (0.10 g, 0.23 mmol) in dry tetrahydrofuran (15 mL) according to the method of preparation of compound **6a**. Thin layer chromatography and elution with dichloromethane afforded the pyrroloindole as a yellow-greenish solid (30 mg, 30 %), m.p. 132-134°C. (Found: C, 58.1; H, 4.3; N, 3.2. $C_{20}H_{16}BrNO_4$ requires C, 58.0; H, 3.9; N, 3.4 %). λ_{max} 211 nm (ε 78700), 329 (21800). ν_{max} 1720, 1600, 1350, 1270, 1240, 1220, 1180 cm^{-1}. ^{1}H n.m.r. ($CDCl_3$): δ 3.98, 3.99 and 4.20, each s, OMe; 6.47, s, H7; 7.53, d, *J* 8.7 Hz, H2'; 7.58, s, H5; 7.77, d, *J* 8.7 Hz, H3'; 7.87, s, H2. ^{13}C n.m.r. ($CDCl_3$): δ 51.9, 56.2and 57.8, OMε; 95.4, C7; 115.9, C5; 119.0, C2; 129.3 and 131.3, ArCH; 102.2, 102.4, 120.4, 125.2, 125.8, 133.7, 141.1 and 158.2, ArC; 161.8, CO. Mass spectrum: *m/z* 416(M+1, ^{81}Br, 20%), 415(M, ^{81}Br, 99), 414(M+1, ^{79}Br, 18), 413(M, ^{79}Br, 100), 319(22), 201(23), 188(29), 183(22), 149(21), 59(28).

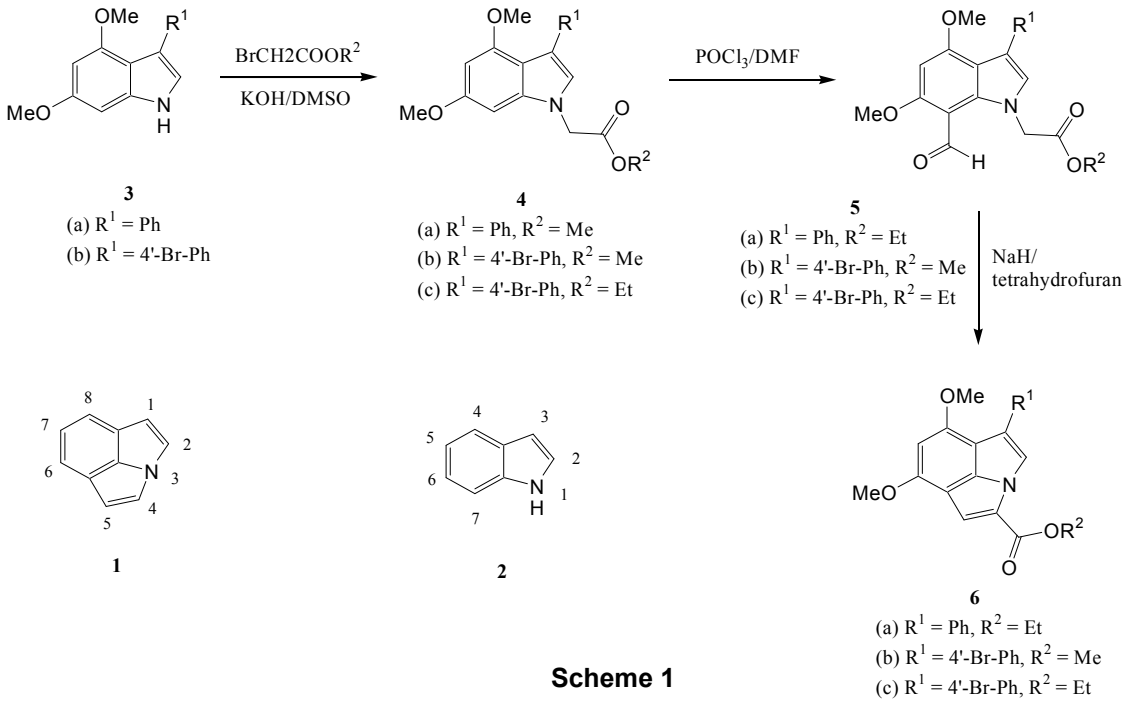
Ethyl 1-(4'-bromophenyl)-6,8-dimethoxypyrrolo-[3,2,1-hi]-indole-4-carboxylate (6c)

Sodium hydride (80 % in paraffin oil, 0.16 g, 5.38 mmol) was reacted with formylindole **5c** (1.20 g, 2.69 mmol) in dry tetrahydrofuran (100 mL) according to the method of preparation of compound **6a**. Flash chromatography and elution with light petroleum in dichloromethane (1:3) afforded the pyrroloindole as a light yellow solid (0.55 g, 48 %), m.p. 164-166°C. (Found: C, 58.8; H, 4.1; N, 3.2. $C_{21}H_{18}BrNO_4$ requires C, 58.9; H, 4.2; N, 3.3 %). λ_{max} 205 nm (ε 5000), 245 (2600), 263 (2000), 334 (2800). ν_{max} 1710, 1580, 1350, 1300, 1260, 1230, 1210 cm^{-1}. ^{1}H n.m.r. ($CDCl_3$): δ 1.50, t, *J* 7.1 Hz, $CH_2C\underline{H}_3$; 4.03 and 4.26, each s, OMe; 4.49, q, *J* 7.1 Hz, $C\underline{H}_2CH_3$; 6.52, s, H7; 7.57 and 7.81, 2d, *J* 6.7 Hz, ArH; 7.63, s, H5; 7.92, s, H2. ^{13}C n.m.r. ($CDCl_3$): δ 14.5, $CH_2\underline{C}H_3$; 56.3 and 58.0, OMe; 61.0, $\underline{C}H_2CH_3$; 74.3, 102.3, 120.5, 125.7, 133.8, 139.4, 153.1, 154.4 and 155.6, ArC; 95.7, C7; 115.9, C5; 119.2, C2; 129.8 and 131.5, ArCH; 158.3, CO. Mass spectrum: *m/z* 430(M+1, ^{81}Br, 19%), 429(M, ^{81}Br, 92), 428(M+1, ^{79}Br, 20), 427(M, ^{79}Br, 100), 401(25), 399(26), 305(30), 290(14), 201(17), 190(19), 81(15), 69(41), 45(16), 43(17).

RESULT AND DISCUSSION

One of the important aspects to be investigated in this work was the development of the Keller strategy in generating pyrroloindoles [12]. The application of such a strategy in the case of 3-aryl-4,6-dimethoxyindoles within this research is as presented in Scheme 1. It is worth mentioning that the *N*-alkylation of the indoles was conducted prior to formylation, since previous work by Black and coworkers [15] has shown that 4,6-dimethoxy-1,2-diphenylindole-7-carbaldehyde failed to undergo allylation at nitrogen. The *N*-alkylation of indoles themselves was carried out using the Heany and Ley method [16] which has more recently been employed in the *N*-allylation [15] and *N*-alkylation [12] of 4,6-dimethoxy-2,3-diphenylindole.

Treatment of the 3-aryl-4,6-dimethoxyindoles **3a** and **3b** with 1.5 equivalents of potassium hydroxide in dimethyl sulfoxide followed by ethyl or methyl 2-bromoacetate afforded alkylindoles **4a-c** in 70-78 %



3
(a) R^1 = Ph
(b) R^1 = 4'-Br-Ph

4
(a) R^1 = Ph, R^2 = Me
(b) R^1 = 4'-Br-Ph, R^2 = Me
(c) R^1 = 4'-Br-Ph, R^2 = Et

5
(a) R^1 = Ph, R^2 = Et
(b) R^1 = 4'-Br-Ph, R^2 = Me
(c) R^1 = 4'-Br-Ph, R^2 = Et

1

2

6
(a) R^1 = Ph, R^2 = Et
(b) R^1 = 4'-Br-Ph, R^2 = Me
(c) R^1 = 4'-Br-Ph, R^2 = Et

Scheme 1

yield. It was observed that the reactions never went to completion despite the use of various conditions, such as sodium hydride in tetrahydrofuran or stirring for 24 hours. When five or more equivalents of potassium hydroxide were employed, the majority of the expected esters hydrolyzed to form the corresponding acids. However, an experiment carried out on the acid showed that the compound could be converted back to the initial ester in almost quantitative yield by a simple esterification in refluxing ethanol in the presence of concentrated sulfuric acid. This was quite interesting as some indoles are known to be unstable under the influence of strong acids.

Clear evidence for the alkyl indoles **4a-c** was provided by the infrared spectra, which demonstrated the absence of NH groups and the presence of carbonyl stretching frequencies. The ^{1}H n.m.r. spectra also confirmed the existence of α-methylene protons which appear as singlets at 4.64, 4.77 and 4.76 ppm for indoles **4a**, **4b** and **4c,** respectively.

Vilsmeier reagents [17-20] have been widely used for the incorporation of formyl functionalities into indoles. While indole itself reacts with the Vilsmeier reagent at the 3-position [21], the activated 4,6-dimethoxyindole undergoes formylation at 10°C to yield the 7-carbaldehyde [22]. Evidence for substitution at C7 rather than at C3 was derived from the ^{1}H n.m.r. spectrum of the product in comparison with that of the previously known 3-carbaldehyde formed from 4,5,6-trimethoxyindole [23]. Double formylation to give the 3,7-dicarbaldehyde was also seen when 4,6-dimethoxyindole was treated with a large excess of the Vilsmeier reagent at 30-40°C.

Exclusive formylation at C7 was found when other reactive centers of the indole were blocked, as in the case of 4,6-dimethoxy-2,3-diphenylindole [24]. When this indole was allylated [15] or alkylated [12], the resulting *N*-substituted indoles were found still to be reactive towards the Vilsmeier reagent to afford the corresponding 7-carbaldehydes. A strong predominance of formylation at C7 over C2 was found when 4,6-dimethoxy-3-phenylindole was reacted with one equivalent of the Vilsmeier reagent [25]. However, the use of two or more equivalents of the reagent readily formed the 2,7-dicarbaldehyde.

Formylation of indoles **4** with 1.5 equivalents of the Vilsmeier reagent at 0°C for 1 hour gave the related 7-carbaldehydes **5** in 54-81 % yield without any of the 2-isomers. No further formylation leading to the 2,7-dicarbaldehyde was observed when four equivalents of the reagent were used. Probably the existence of the alkyl groups at N1 causes a significant steric hindrance at C2 which is sufficient to inhibit its reactivity towards the Vilsmeier reagent.

Clear evidence for the formyl products was given by the ^{1}H n.m.r. spectra in which the two typical doublets corresponding to H5 and H7 of the starting materials disappeared and were replaced by two singlets due to H5 and the formyl proton. The latter appeared at 10.71, 10.23 and 10.39 ppm for formylindoles **5a**, **5b** and **5c,** respectively.

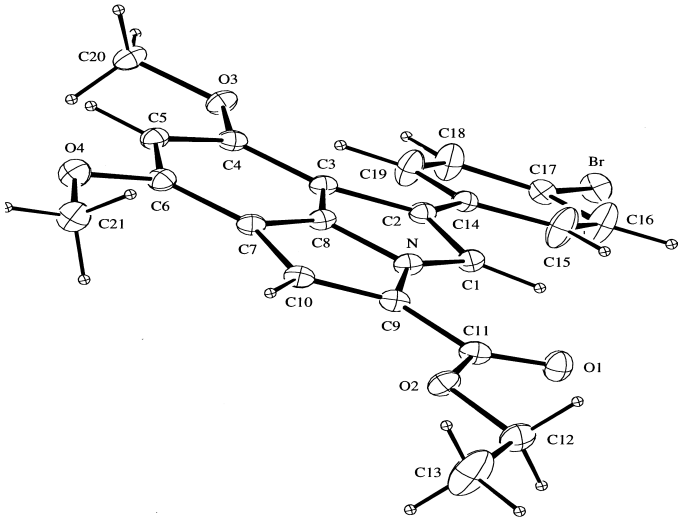


Fig 1. X-ray crystal structure of pyrroloindole **6c**

Treatment of formylindoles **5** with two equivalents of sodium hydride in refluxing tetrahydrofuran for 2 hours afforded moderate yields of ethyl pyrroloindoles **6a** (60 %) and **6c** (48 %), and only a 30 % yield of the methyl analogue **6b**. The last pyrroloindole was obtained in a low yield presumably because of the insolubility of the aldehyde precursor. Another possible reason could be the instability towards hydrolysis of the methyl ester in comparison with the ethyl ester. However, no free acids were isolated. In general, the formation of the pyrroloindoles could be easily monitored by means of thin layer chromatography as the compounds give green or yellow-greenish fluorescence under far UV light.

The pyrroloindoles **6** were characterized fully. For example, the ^{1}H n.m.r. spectrum of pyrroloindole **6c** showed the replacement of two singlets at 5.33 and 10.37 ppm corresponding to the acetyl CH_2 and formyl proton respectively in the ^{1}H n.m.r. spectrum of the starting material with a singlet at 7.63 ppm originating from H5. The mass spectrum revealed a molecular ion at 429 (^{81}Br, 92 %) and showed the existence of a bromine isotope effect. A significant decrease of the carbonyl stretching frequency from 1750 cm^{-1} in the starting material to 1710 cm^{-1} in pyrroloindole **6c** was observed in the infrared spectrum. Moreover, other analytical and spectroscopic data were consistent with the structure.

Pyrroloindoles **6** are all crystalline and an excellent crystal of pyrroloindole **6c** was obtained by recrystallization from toluene. The X-ray crystal structure of this compound (Figure 1) showed that the pyrroloindole ring is approximately planar as indicated by the torsional angles C1-C2-C3-C8 (0.1°) and C6-C7-C8-N (177.9°). The phenyl ring of the 4'-bromophenyl group and both of the methoxy methyl substituents are about parallel with the pyrroloindole ring as defined by the torsional angles C3-C2-C11-C12 (176.1 °C), C3-C4-O1-C17 (178.6 °C) and C5-C6-O2-C18 (176.6 °C). The 8-methoxy group is directed away from the phenyl ring and the 6-methoxy group which indicates that a significant degree of steric hindrance exists between those substituents. It is also interesting to note that the bond lengths and bond angles of the two pyrrolic rings are similar.

The aldol condensation above was found to be time dependent. When the reaction was conducted at reflux for less than 2 hours, only low yields of pyrroloindoles were obtained together with unreacted starting materials. Similarly, not much improvement was observed when the reaction was carried out at reflux for 4 hours even though all starting materials had reacted. Therefore, the resulting pyrroloindoles seemed to be unstable in such vigorous conditions and underwent further reactions leading to uncharacterized products. Indeed, it was observed that neither pyrroloindoles nor starting materials could be isolated when the reactions were carried out at reflux for 7 hours.

Various reaction conditions have been tried in order to maximize the yield. It was found that the starting material remained intact when weaker bases such as triethylamine, piperidine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were used instead of sodium hydride. On the other hand, removal of the carboxy methyl group was seen when stronger bases such as potassium hydride or *n*-butyl lithium were employed.

CONCLUSION

3-Aryl-4,6-dimethoxyindole **3a** and **3b** underwent alkylation under treatment with methyl and ethyl α-bromoacetates in the presence of potassium hydroxide in dimethylsulfoxide to afford 70-78 % yield of indol-1-ylacetates **4**. These indoles **4** react with the Vilsmeier formylation reagent consisted of phosphoryl chloride and dimethylformamide to give formylindoles **5** in 54-81 % yield. Intramolecular aldol condensation of formylindole **5** carried out using sodium hydride in tetrahydrofuran afforded pyrroloindole-4-carboxylates **6** in 30-60 % yield. The X-ray crystal structure of pyrroloindole **6c** showed that the tricyclic ring system of this molecule is planar.

ACKNOWLEDGEMENT

The author deeply thanks to Prof. David St. C. Black and Dr. Naresh Kumar, both of University of New South Wales Sydney-Australia, for their suggestions and assistance. Financial support from Australian Assistance for International Development (AusAID) for the implementation of this research is also greatly appreciated.

REFFERENCES

1. Pomeroy, A.R., and Raper, C., 1971, *Eur. J. Pharmacol.*, *14*, 374-383.
2. Lathbury, D.C., Parsons, P.J., and Pinto, I., 1988, *J. Chem. Soc., Chem. Commun.*, 81-82.
3. Anet, F.A.L., Muchowski, J.M., and Nishizawa, E., 1961, *Chem. & Ind. (London)*, 1117.
4. Robinson, B., 1963, *Chem. Rev.*, *63*, 373-401.
5. Robinson, B., 1968, *Chem. Rev.*, *68*, 227-250.
6. Van Order, R.B., and Lindwall, H.G., 1941, *Chem. Rev.*, *41*, 69-96.
7. Paudler, W.W., and Shin, H.G., 1969, *J. Heterocycl. Chem.*, *6*, 415-417.
8. Ishii, H., Takeda, H., Hagiwara, T., Sakamoto, M., and Kogusuri, K., 1989, *J. Chem. Soc. Perkin Trans. 1*, 2407-2414.
9. Brown, D.W., Mahon, M.F., Ninan, A., Sainsbury, M., and Shertzer, H.G., 1993, *Tetrahedron*, *49*, 8919-8932.
10. Bartsch, H., 1976, *Monatsh. Chem.*, *107*, 663-667.
11. Bartsch, H., 1981, *Monatsh. Chem.*, *112*, 1451-1457.
12. Keller, P.A., 1991, *Ph.D Thesis,* University of New South Wales,.
13. Still, W.C., Kahn, M., and Mitra, A., 1978, *J. Org. Chem.*, *43*, 2923-2925.
14. Black, D.StC, Bowyer, M.C., Bowyer, P.K., Ivory, A.J., Kim, M., Kumar, N., McConnell, D.B., and Popiolek, M., 1994, *Aust. J. Chem.*, *47*, 1741-1750.
15. Black, D.StC., Keller, P.A., and Kumar, N., 1993, *Aust. J. Chem.*, *46*, 843-862.
16. Heaney, H., and Ley, S.V., 1973, *J. Chem. Soc. Perkin Trans. I*, 499-500.
17. Seshadri, S., 1973, *J. Scient. Ind. Res.*, *32*, 128-149.
18. Marson, C.M., 1992, *Tetrahedron*, *48*, 3659-3726.
19. Meth-Cohn, O., and Stanforth, S.P, 1991, *Comprehensive Organic Chemistry*, Vol. 2, Trost, B.M. Fleming, I., Chief Ed. Heathcock, C.H., Vol. Ed., Pergamon Press, Oxford, p.777-794.
20. Meth-Cohn, O., and Tarnowski, B., 1982, *Adv. Heterocycl. Chem.*, *31*, 207-236.
21. Joule, J.A., and Smith, G.F., 1978, *Heterocyclic Chemistry*, Van Nostrand Reinhold (International), Second edition, Great Britain, p. 279-283.
22. Brown, V.H., Skinner, W.A., and De Graw, J.I. 1969, *J. Heterocycl. Chem.*, *6*, 539-543.
23. Carlsson, A., Carrodi, H., and Magnusson, T., 1963, *Helv. Chim. Acta*, *46*, 1231-1235.
24. Black, D.StC., Kumar, N., and Wong, L.C.H., 1986, *Synthesis*, 474-476.
25. Black, D.StC. Bowyer, M.C., Kumar, N., and Mitchell, P.S.R., 1993, *J. Chem. Soc., Chem. Commun.*, 819-821.