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-h]INDOLE-4-CARBOXYLATES

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Received 10 May 2006; Accepted 6 June 2006

ABSTRACT

Alkylation of 3-aryl-4,6-dimethoxyindole 3a and 3b with methyl and ethyl α-bromooacetates 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-h]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-h]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-h]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-aminoindolone. The pyrroloindole was obtained in 20% yield and its elemental analysis was in agreement with the proposed structure. The 1H n.m.r. spectrum showed the presense of three aromatic protons appearing as seven lines of an AB2 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-h]indole 1 from the corresponding N-aminoindolone. 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 1H 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 aryldrazines 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-h]indole. When the reaction was carried out at 130°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-h]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-dimethoxydibenzo[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-dimethoxynidoles. Apart from spectroscopic data, the structure of the synthesized pyrroloindole was also proven on the basis of X-ray crystal structure.

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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. ¹H n.m.r. and ¹³C n.m.r. spectra were recorded in the designated solvents on a Bruker AC300F (300 MHz) or a Bruker AM500 (500 MHz) spectrometer. Chemical shifts were determined on the δ scale internally referenced to the solvent peaks: CDCl₃ (7.30 ppm, 77.7 ppm) and DMSO-d₆ (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 using 20x20x0.1 cm plates using Merck silica gel 7730, and refers to the technique of applying suction at the base of the column. Suction chromatograph

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 mmol, 13.30 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. 125°C. (Found: C, 56.5; H, 4.5; N, 3.4. C₂₁H₁₈BrNO₄ requires C, 56.5; H, 4.5; N, 3.5 %). λmax 210 nm (ε 19300), 230 (19500), 280 (106000), 289 (9300). νmax 1740, 1620, 1590, 1330, 1280, 1210, 1170, 1140, 1010 cm⁻¹. ¹H n.m.r. (CDCl₃): δ 3.77, 3.80 and 3.87, each s, OMe; 4.77, s, CH₂; 6.30, s, H₅; 6.32, s, H₇; 6.89, s, H₂; 7.47, s, ArH. ¹³C n.m.r. (CDCl₃): δ 47.9, CH₂; 52.6, 55.1 and 55.7, OMe; 85.1, C₅; 92.4, C₇; 110.6, 117.7, 119.7, 134.7, 139.0, 155.2 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 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. C₁₉H₁₉NO₄ requires C, 70.1; H, 5.9; N, 4.3 %). λmax 208 nm (ε 23200), 224 (27640), 269 (10800), 279 (11280). νmax 1750, 1580, 1270, 1210, 1200, 1160, 1040, 770, 700 cm⁻¹. ¹H n.m.r. (CDCl₃): δ 3.64, 3.69, 3.76, each s, OMe; 4.64, s, CH₂; 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'. ¹³C n.m.r. (CDCl₃): δ 47.9, CH₂; 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).

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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; C₂₀H₂₀BrNO₄ requires C, 57.4; H, 4.8; N, 3.4 %). λₘₐₓ max 208 nm (ε 29800), 223 (31000), 231 (25400), 284 (13500), 299 (12100). vₘₐₓ 1740, 1620, 1280, 1220, 1200, 1160, 790 cm⁻¹. ¹H n.m.r. (CDCl₃): δ 1.28, t, J 7.1 Hz, CH₃CH₂; 3.80 and 3.86, each s, OMe; 4.24, q, J 7.1 Hz, CH₂CH₃; 4.76, s, CH₂; 6.28, d, J 2.0 Hz, H₅; 6.31, d, J 2.0 Hz, H₇; 6.91, s, H₂; 7.47, s, ArH. ¹³C n.m.r. (CDCl₃): δ 14.2, CH₂; 48.1, CH₂; 55.2 and 55.7, OMe; 61.8, CH₂CH₃; 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, CO₂Et. Mass spectrum: m/z 419(M⁺, 13%), 417(M, 79Br, 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-ylacetate (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, 6.33 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 phosphoril chloride (0.3 ml, 2.94 mmol) in dry dimethylformamide (1.0 ml) was added dropwise. The mixture was stirred at 0°C 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. C₂₁H₂₁NO₅ requires C, 68.7; H, 5.8; N, 3.8 %). λₘₐₓ max 216nm (ε 9900), 233 (9900), 262 (11000), 337 (7200). vₘₐₓ 1755, 1650, 1590, 1570, 1555, 1280, 1225, 1210 cm⁻¹. ¹H n.m.r. (CDCl₃): δ 1.29, t, J 8.2 Hz, CH₃CH₂; 3.82 and 3.93, each s, OMe; 4.22, q, J 8.2 Hz, CH₂CH₃; 5.33, s, CH₂; 6.21, s, H₅; 6.80, s, 2; 7.31, m, H₂'2'; 7.51, d, J 9.1 Hz, H₄'; 10.39, s, CHO. ¹³C n.m.r. (CDCl₃): δ 14.1, CH₂; 53.1, CH₂; 55.1 and 56.8, OMe; 61.1, CH₂CH₃; 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 phosphoril 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 formylinindle as a brown solid (0.51g, 73 %), m.p. 243-245°C. (Found: C, 55.3; H, 4.3; N, 3.1. C₂₀H₁₈BrNO₅ requires C, 55.6; H, 4.2; N, 3.2 %). λₘₐₓ max 212 nm (ε 18400), 227 (17200), 257 (10300), 281 (5800). vₘₐₓ 1770, 1600, 1590, 1570, 1280, 1225 cm⁻¹. ¹H n.m.r. (DMSO-d₆): δ 3.63, 3.90 and 3.98, each s, OMe; 5.33, s, CH₂; 6.54, s, H₅; 7.24, s, H₂; 7.38 and 7.53, 2d, J 7.8 Hz, ArH; 10.23, s, CHO. ¹³C n.m.r. (DMSO-d₆): δ 52.0, 55.8 and 57.3, OMe; 52.4, CH₂; 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⁺, 81Br, 14%), 432(M⁺+1, 79Br, 12), 431(M⁺, 79Br, 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 phosphoril 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 formylinindle as a white solid (0.54 g, 81 %), m.p. 209-211°C. (Found: C, 56.5; H, 4.5; N, 3.0. C₂₁H₂₀BrNO₅ requires C, 56.5; H, 4.5; N, 3.1 %). λₘₐₓ max 208 nm (ε 10700), 234 (8700), 259 (11200), 333 (4100). vₘₐₓ 1750, 1650, 1580, 1550, 1270, 1210, 810, 780 cm⁻¹. ¹H n.m.r. (CDCl₃): δ 1.28, t, J 7.1 Hz, CH₂CH₃; 3.86 and 3.96, each s, OMe; 4.22, q, J 7.1 Hz, CH₂CH₃; 5.33, s, CH₂; 6.24, s, H₅; 6.79, s, H₂; 7.35 and 7.46, 2d, J 8.5 Hz, ArH; 10.71, s, CHO. ¹³C n.m.r. (CDCl₃): δ 14.2, CH₂; 53.2, CH₂; 55.3 and 57.0, OMe; 61.3, CH₂CH₃; 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;
Ethyl 6,8-dimethoxy-1-phenylpyrrolo[3,2,1-hijindole-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. 132-134°C. (Found: C, 71.9; H, 5.6; N, 3.9. C_{21}H_{19}BrN_{10}O_4 requires C, 72.2; H, 5.5; N, 4.0 %).

Ethyl 1-(4’-bromophenyl)-6,8-dimethoxypyrrrolo-[3,2,1-hij-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}BrN_{10}O_4 requires C, 58.9; H, 4.2; N, 3.3 %). $\lambda_{max}$ 212 nm ($\varepsilon$ 58000), 236 (45500), 265 (24000), 333 (52500). $\lambda_{max}$ 1710, 1580, 1350, 1300, 1260, 1230, 1210 cm$^{-1}$. $^1$H n.m.r. (CDCl$_3$): $\delta$ 1.50, t, J 7.1 Hz, CH$_2$CH$_3$; 4.03 and 4.26, each s, OMe; 56.3 and 57.9, OMe; 61.0, CH$_2$CH$_3$; 93.50, 103.62, 104.04, 122.44, 126.82, 127.40, 134.25 and 158.05, ArC; 161.8, CO. $\lambda_{max}$ 211 nm ($\varepsilon$ 78000), 329 (21800). $\lambda_{max}$ 1720, 1600, 1350, 1270, 1240, 1220, 1180 cm$^{-1}$. $^1$H n.m.r. (CDCl$_3$): $\delta$ 3.98, 3.99 and 4.20, each s, OMe; 6.47, s, H$_7$; 7.53, d, J 8.7 Hz, H$_2$; 7.58, s, H$_5$; 7.77, d, J 8.7 Hz, H$_3$; 7.87, s, H$_2$. $^{13}$C n.m.r. (CDCl$_3$): $\delta$ 51.9, 56.2 and 57.8, OMe; 95.4, C$_7$; 115.9, C$_5$; 119.0, C$_2$; 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, 81Br, 20%), 415(M, 81Br, 99), 414(M+1, 79Br, 18), 413(M, 79Br, 100), 319(22), 201(23), 188(29), 183(22), 149(21), 59(28).

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-arylidene-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 alkylation 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-alkylation [15] and N-alkylation [12] of 4,6-dimethoxy-2,3-diphenylindole.

Treatment of the 3-arylidene-4,6-dimethoxyindoles 3a and 3b with 1.5 equivalents of potassium hydroxide in dimethyl sulfoxide followed by ethyl or methyl 2-bromoacetoacetate afforded alkylindoles 4a-c in 70-78 %.
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 $\alpha$-methylene protons which appear as singlets at 6.46, 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.

Scheme 1
Treatment of formylindole 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 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-yacetates 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.
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