SYNTHESIS OF NEW ACTIVATED INDOLES; 3-(4'-BROMOPHENYL)-4,6-DIMETHOXY-2-METHYLINDOLE

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ABSTRACT

3-(4'-Bromophenyl)-4,6-dimethoxy-2-methylindole has been synthesized from 4,6-dimethoxyaniline via the modified Bischler method. Reaction of 4,6-dimethoxyaniline with 2,4-dibromopropiophenone gave an aniline ketone in 85%, and then it was protected to give the amido ketone as a white solid. Cyclization of amido ketone was performed by trifluoroacetic acid and subsequent deprotection with potassium hydroxide in methanol afforded a white solid of 3-(4'-bromophenyl)-4,6-dimethoxy-2-methylindole in 86%.

Keywords: 4*,6-dimethoxyaniline, 2-methylindole, Bischler method*

INTRODUCTION

The indole heterocyclic system is present in many naturally occurring alkaloids, which exhibit interesting biological activities. Recently, the simple indole 3-carbinol (I3C), a constituent of cruciferous vegetables such as cabbage, cauliflowers and broccoli has been shown to have a cytotoxic effect in prostate [1], colon [2] and also human breast cancer cells [3]. Indoles containing electron donating methoxy groups have also been found in nature. For example, indomethacine is an anti-inflammatory agent for the gastrointestinal tract [4] and carbazomycins demonstrate antibiotic activity [5].

In conjunction with the synthetic efforts on activated indoles, the activation at C7 can be generated by electron donating methoxy groups at position 4 and 6 on the indole ring.

The first synthesis of 4,6-dimethoxyindole was carried out by the reduction of 4,6-dimethoxyisatin with lithium aluminium hydride [6]. In order to search for a range of new indoles, the chemistry of substituted 4,6-dimethoxyindoles was investigated by Black [7,8] and the 2,3-disubstituted [8] and 2-substituted [7] activated indoles have been synthesised by the use of the Bischler technique.

The classical problem of the Bischler technique is the rearrangement during the cyclization of the secondary phenacylaniline, in the presence of a trace amount of aniline hydrobromide to give the 2-phenylindole. Crowther and Mann [9] found that *N*-substituted phenacylaniline could be cyclized to give the 3-substituted indole without any rearrangement product. Furthermore, Nordlander *et al* [10] reported that the nitrogen atom of the anilino ketone could be protected by reaction with trifluoroacetic anhydride. Based on these results, a modified Bischler synthesis has been carried out to produce some activated 3-arylindoles with a variety of electronic character at C4 of the aryl group [11].

It has also been reported that 2,2'-diindolylmethanes **1** have been synthesized by acid catalyzed addition of formaldehyde to the corresponding activated indole[12]. These compounds have been useful precursors to a range of 15-membered macrocyclic ligands and metal complex catalysts. It was of interest to investigate slightly enlarged 16-membered ring systems, in terms of any modified properties. This required the synthesis of the 2,2'-diindolylethane **2** as a suitable precursor. However, in an initial study, the 2–methyl-3-arylindole **3** could be used as a model to investigate the reactivity of an activated 2-alkyl indole (Scheme 1). In this paper, the synthesis of 2-methyl-3-aryl indole **3a** via modified Bischler techniques will be reported.

EXPERIMENTAL SECTION

General

Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Elemental analyses were performed by The Campbell Microanalytical Laboratory, University of Otago, New Zealand. Infrared spectra were obtained on a Mattson Genesis series FTIR spectrometer. Ultraviolet spectra were measured on Carey 100 spectrophotometers and refer to solutions in

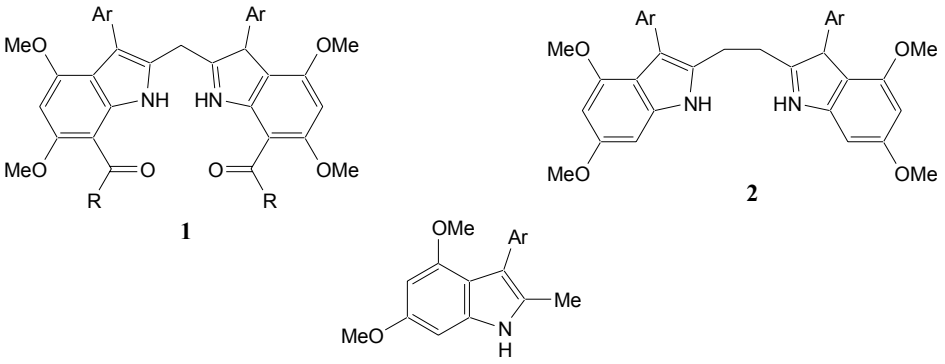

Fig 1 Scheme 1

absolute methanol. ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz with a Bruker AC300F or at 500MHz with a Bruker AM500 spectrometer and the chemical shifts are referenced to internal solvent resonances. The EI mass spectra were measured using a VG Quattro mass spectrometer .

1-(4-Bromophenyl)-2-[(3,5-dimethoxyphenyl)amino] propanone (5)

3,5-Dimethoxyaniline (5.00 g, 32.6 mmol), 2,4'-di-bromopropiophenone (9.56 g, 32.7 mmol) and sodium hydrogen carbonate (2.72 g, 32.4 mmol) were added to absolute ethanol (100 ml) and refluxed for 5h. The mixture was allowed to cool to room temperature and the resulting yellow precipitate was filtered off, washed with water and dried to yield the *title compound* **5** (10.10 g, 85%) as a pale-yellow solid. Recrystallization from ethyl acetate/light petroleum resulted in pale yellow needles. m.p. 159-160°C. (Found : C, 55.8; H, 5.2; N, 3.8. $C_{17}H_{18}BrNO_3$ requires C, 56.0; H, 4.9; N, 3.8%). ν_{max} : 3402, 1687, 1619, 1583, 1479, 1199, 1168, 1070, 958 cm^{-1}. λ_{max} : 228 nm (ε 17,350 cm^{-1} M^{-1}), 263 (16,950). δ_H (300 MHz, $CDCl_3$) 1.46 (3H, d, *J* 7.2 Hz, CH_3), 3.73 (6H, s, OCH_3), 5.01 (1H, q, *J* 6.8 Hz, C<u>H</u>CH_3), 5.87, 5.90 (3H, 2d, *J* 1.9 Hz, H2, H4, H6), 7.64, 7.85 (4H, 2d, *J* 8.7 Hz, ArH). δ_C (75 MHz, $CDCl_3$) 19.2 (CH_3), 53.7 (CH), 55.1 (OCH_3), 90.7, 92.8, 129.8, 132.1 (ArCH), 128.8, 133.2, 147.6, 161.7 (ArC), 199.1 (C=O). Mass spectrum (EI) : *m/z* 366 (M+2, ^{81}Br, 1%), 365 (2), 364 (M, ^{79}Br, 1), 363 (2), 180 (100), 165 (3).

***N*-Acetyl-1-(4-bromophenyl)-2-[(3,5-dimethoxyphenyl)amido] propanone (6)**

The anilino ketone **5** (0.40 g, 1.10 mmol) was partially dissolved in acetic anhydride (2 ml) and heated at 50°C overnight. Water was then added slowly so that temperature did not drop below 50°C until the volume was tripled. Stirring was continued until the solution returned to room temperature. The solution was then extracted with ethyl acetate and the organic phase was washed with saturated sodium hydrogen carbonate solution and water until neutral, and then dried. The solvent was evaporated off to give the *title compound* **6** (0.41 g, 92%) as an off white solid. m.p. 140-141°C.(Found : C, 56.3; H, 4.8; N, 3.6. $C_{19}H_{20}BrNO_4$ requires C, 56.2; H, 5.0; N, 3.5%). ν_{max} : 1689, 1654, 1592, 1324, 1203, 1162, 1071 cm^{-1}. λ_{max} : 228 nm (ε 14,800 cm^{-1} M^{-1}), 258 (20,900). δ_H (300 MHz, $CDCl_3$) 1.23 (3H, d, *J* 7.2 Hz, CH_3), 1.85 (3H, s, $COCH_3$), 3.72 (6H, s, OCH_3), 6.06 (1H, q, *J* 7.2 Hz, CH), 6.26 (2H, d, *J* 2.3 Hz, ArH), 6.43 (1H, t, *J* 2.3 Hz, ArH), 7.62, 7.89 (4H, 2d, *J* 8.7 Hz, ArH). δ_C (75 MHz, $CDCl_3$) 14.9, 22.5 (CH_3), 54.9 (CH), 55.4 (OCH_3), 100.4, 108.1, 129.9, 131.9 (ArCH), 128.2, 134.5, 140.6, 160.9 (ArC), 170.4, 198.0 (C=O). Mass spectrum (EI) : *m/z* 408 (M+2, ^{81}Br, 100%), 407 (86), 406 (M, ^{79}Br, 92), 405 (51), 363 (16), 383 (40), 236 (47).

1-Acetyl-3-(4-bromophenyl)-4,6-dimethoxy-2-methylindole (7)

The amido ketone **6** (9.40 g, 23.1 mmol) was dissolved in trifluoroacetic acid (32 ml). The solution was stirred overnight after which ice/water was added and the mixture was extracted with dichloromethane, washed with water until neutral and dried. The solvent was evaporated under reduced pressure and the residue was chromatographed with dichloromethane to afford the *title compound* **7** (6.87 g, 77%) as a white solid. m.p. 172°C. (Found : C, 58.4; H, 4.6; 3.6 $C_{19}H_{18}BrNO_3$ 0.1 H_2O requires C, 58.5; H, 4.7; N, 3.6%). ν_{max} : 1687, 1595, 1571, 1495, 1418, 1370, 1293, 1216, 1151 cm^{-1}. λ_{max} : 208 nm (ε 39,350 cm^{-1} M^{-1}), 248 (23,600), 319 (4,950). δ_H (300 MHz, $CDCl_3$) 2.40 (3H, s, CH_3), 2.71 (3H, s, $COCH_3$), 3.62, 3.87 (6H, s, OCH_3), 6.34 (1H, d, *J* 2.3 Hz, H5), 7.38 (1H, d, *J* 1.9 Hz, H7), 7.21, 7.50 (4H, 2d, *J* 8.3 Hz, ArH). δ_C (75 MHz, $CDCl_3$) 14.9, 27.4 (CH_3), 55.1, 55.7 (OCH_3), 92.6 (C5), 94.9 (C7), 130.3, 132.5 (ArCH), 112.6, 120.7, 120.8, 129.8, 134.0, 137.6, 153.4, 158.6 (ArC), 170.7 (C=O). Mass spectrum (EI) : *m/z* 390

(M+2, ^{81}Br, 100), 388 (M, ^{79}Br, 100), 348 (56), 346 (60).

3-(4-Bromophenyl)-4,6-dimethoxy-2-methylindole (3a)

The N-acetylindole **7** (4.91 g, 12.65 mmol) was partially dissolved in methanol (25 ml). An excess of crushed potassium hydroxide was added to the above mixture and allowed to stir overnight. The resulting precipitate was filtered off, washed and dried to yield the *title compound* **3a** as a white solid (3.78 g, 86%), m.p. 162-163^{o}C. (Found : C, 58.7; H, 4.5; N, 4.1. $C_{17}H_{16}BrNO_2$ requires C, 58.9; H, 4.7; N, 4.1%). ν_{max} : 3338, 1620, 1561, 1487, 1340, 1319, 1217, 1199, 1151, 1129, 814 cm^{-1}. λ_{max} : 232 nm (ε 22,950 cm^{-1} M^{-1}). δ_H (300 MHz, $CDCl_3$) 2.30 (3H, s, CH_3), 3.70, 3.82 (6H, 2s, OCH_3), 6.22 (1H, s, H5), 6.42 (1H, s, H7), 7.29, 7.48 (4H, 2d, *J* 8.2 Hz, ArH), 7.84 (1H, br, NH). δ_C (75 MHz, $CDCl_3$) 11.9 (CH_3), 54.9, 55.6 (OCH_3), 86.6 (C5), 91.9 (C7), 130.1, 132.5 (ArCH), 111.4, 112.9, 119.4, 129.0, 134.9, 136.7, 154.0, 156.9 (ArC). Mass spectrum (EI) : *m/z* 348 (M+2, ^{81}Br, 12%), 347 (100), 346 (M, ^{79}Br, 12), 345 (98), 332 (29), 330 (29), 266 (8), 251 (86).

RESULTS AND DISCUSSION

Treatment of 3,5-dimethoxyaniline with 2,4'-dibromopropiophenone under reflux for 5 hours in ethanol containing sodium hydrogen carbonate yielded the anilino ketone **5** as a yellow solid. This was then treated with acetic anhydride to give the protected anilino ketone **6** in high yield.

The ^{1}H NMR spectrum of anilino ketone **5** confirms the presence of the CH_3 protons as a doublet at 1.46 ppm and the CH proton appear as a kuartet at 5.01 ppm. The ^{13}C NMR spectrum demonstrated signals at 53.7 and 170.8 ppm originating from the corresponding methyl and carbonyl carbon respectively.

The acetyl protons were found in the ^{1}H NMR spectrum of the amido ketone **6** as a singlet at 1.85 ppm and the CH proton was shifted downfield to 6.06 ppm with respect to 5.01 ppm in the starting material due to electron withdrawing of acetyl group. In addition the corresponding molecular ion was observed at *m/z* 406 (^{79}Br, 92%) in the mass spectrum.

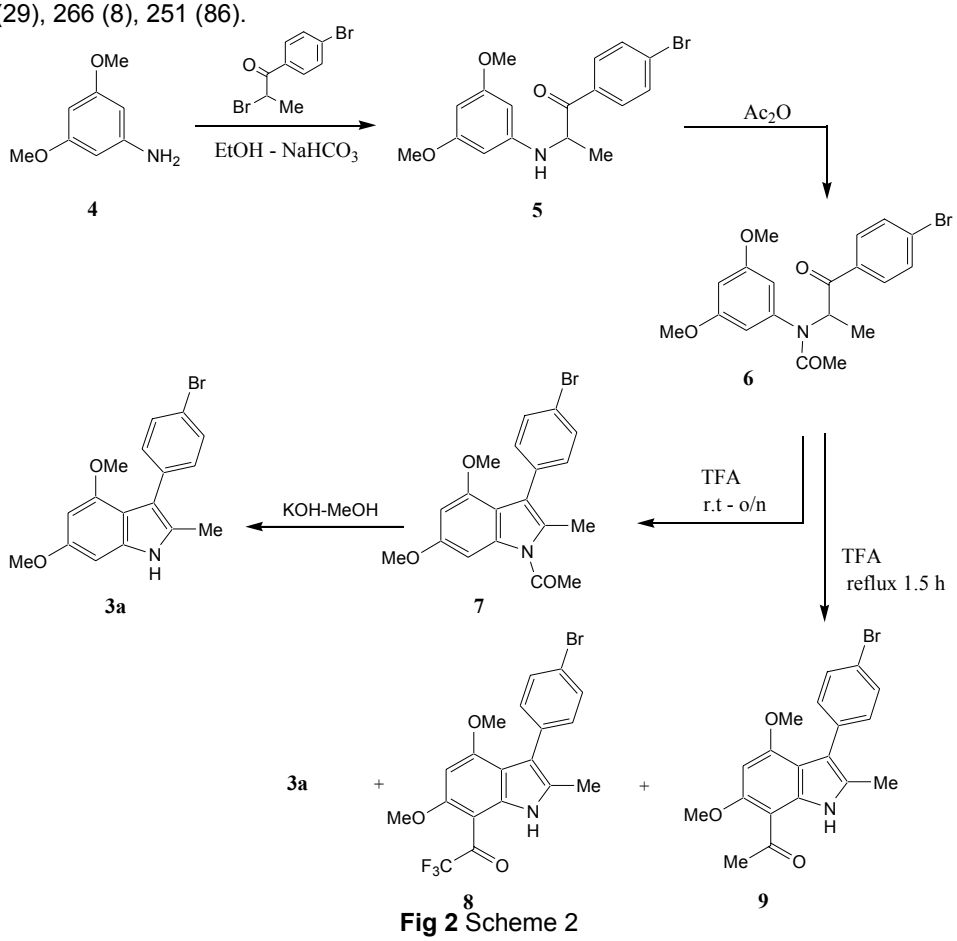

Fig 2 Scheme 2

The cyclization step in the synthesis of 3-arylindoles usually is carried out by the use of trifluoroacetic acid under reflux for one hour. However, similar treatment of the protected anilino ketone **6** produced the deprotected indole **3a** in 31% together with trifluoroacetylindole **8** and acetylindole **9** in 29 and 17% yield respectively. This is understandable as presumably the reaction conditions are too harsh so that cyclisation was easily followed by deprotection and subsequent acylation by the available electrophiles. When a similar reaction was performed at room temperature overnight it give the desired protected indole **7**. It was observed that the crude product also contained some unreacted starting material together with the indole **3a** and complete removal of the starting material was important in order to give a cleaner product from the next deprotection step. In addition, it was found that after 2 days stirring, almost all of the starting material had been consumed and the reaction gave a high yield of the product even though it still contained some indole **3a**.

Clear evidence of protected indole **7** was given by the ^{1}H NMR spectrum, which demonstrated the presence of singlet peak for CH_3 protons at 2.40 ppm and a sharp singlet peak at 2.71 ppm corresponding to a molecular ion at *m/z* 388 (^{79}Br, 100%) and *m/z* 346 from the loss of an acetyl group.

Unlike the 2-unsubstituted-3-arylindole analogs, deprotection of indole **7** needs a longer time for completion. Therefore, the protected indole **7** and potassium hydroxide in methanol needed stirring at room temperature overnight to give the indole **3a** in 86% yield as a white solid.

The mass spectrum of indole **3a** revealed a molecular ion at *m/z* 346 (^{79}Br, 12%) and the elemental analysis was consistent with the assigned structure. The ^{1}H NMR spectrum showed a singlet at 2.30 ppm corresponding to the C2 methyl protons, two singlets for H5 and H7 appearing at 6.22 and 6.42 ppm respectively, whereas the resonance of the NH appeared as a broad signal at 7.84 ppm.

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