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# Simple Syntheses Of 5-Fluoro/Chloro/ Bromoindole-2-Methanols And 5-Fluoro/Chloro/Bromoindole-2-Aldehydes

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## ABSTRACT

Efficient and simple methods for the syntheses of 5-flouro/chloro/ bromoindole-2-methanols and 5-flouro/chloro/bromoindole-2-aldehydes have been described. 5-Flouro/chloro/bromoindole-2-methanols were prepared by the reduction of methyl-5-flouro/chloro/bromoindole-2-carboxylates with sodium borohydride in methanol/tetrahydrofuran media and 5-fluoro/chloro/bromoindole-2-aldehydes were prepared from 5-flouro/chloro/bromoindole-2-methanols by the oxidation with PCC (pyridinium chlorochromate) or with chromium trioxide-pyridine prepared *in situ*. The compounds have been isolated in good yields and characterized by $^{1}H$ NMR, $^{13}C$ NMR, FABMS and elemental analysis.


## KEYWORDS

Syntheses;
5-Flouro/chloro/ bromoindole-2-methanol;
5-Flouro/chloro/ bromoindole-2-aldehydes.

## INTRODUCTION

Indole nucleus is a structural unit found in many natural products and many of the biologically active molecules[1]. Synthesis of indole-2-methanol is reported by using lithium aluminium hydride[2] and is less known in the literature using sodium borohydride. Reduction of aromatic esters to alcohols can be conveniently done by using sodium borohydride in good yields[3]. The synthesis of 5-haloindole-2-methanols has been reported in the literature using lithium aluminium hydride and not using sodium borohydride[4].

Chromic acid in a variety of acidic media, has been used extensively for the oxidation of primary alcohols to aldehydes but rarely has provided alde-

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hydes in greater than 50% yield[5]. Collins and coworkers found that anhydrous dipyridine-chromium (IV) oxide is moderately soluble in chlorinated hydrocarbons and chosen dichloromethane as solvent. With this modification, primary and secondary alcohols were oxidized to aldehydes and ketones in yields of 87-98%. The main problems in preparing this reagent are the nuisance involved in preparing pure dipyridine-chromium (IV) oxide, its hygroscopic nature, and propensity to inflame during preparation[6]. The preparation of chromium trioxide-pyridine complex *in situ* avoids the above-mentioned difficulties[7].

Syntheses of indole-2-aldehydes were reported by the oxidation of potassium permanganate in acetone[8] and also by the reduction of corresponding acid chlorides with lithium aluminium tri t-butoxyhydride[9]. Recently, we have reported a simple and cost effective method for the synthesis of 4,5-,6-,7- nitroindole-2-methanols starting from ethyl 4,5-,6-,7-nitroindole-2-carboxylates by using sodium borohydride in methanol / tetrahydrofuran media and further oxidation to 4,5,6,7-nitroindole-2-aldehydes with PCC (pyridinium chlorochromate) or with chromium trioxide-pyridine prepared *in situ* respectively[10].

As a continuation of our studies, we aimed at the reduction of methyl esters of 5-fluoro/ chloro/ bromoindole-2-cabroxylic acids to corresponding 5-fluoro/ chloro/ bromoindole-2-methanols using sodium borohydride-methanol system (SCHEME 1). This methodology is simple, inexpensive and the selective reduction of esters was completed within 2-3h after refluxing in THF. All the compounds were characterized by spectral and elemental analysis. We also developed facile and efficient methods for the oxidation of 5-fluoro/chloro/bromoindole-2-methanols to 5-fluoro/chloro/bromoindole -2-aldehyde with PCC (pyridinium chlorochromate) and chromium trioxide-pyridine complex prepared *in situ* (SCHEME 1). The present methods are very simple, safe and superior over the other methods reported for the oxidation of indole-2-methanols. All the compounds are well characterized by spectral and elemental analysis. Yields obtained with PCC are comparable with chromium trioxide-pyridine system. Both the methods are viable for large-scale preparation of 5-fluoro/chloro/bromoindole-2-aldehydes. Characterization data of all the compounds are given in TABLE 1.

## EXPERIMENTAL

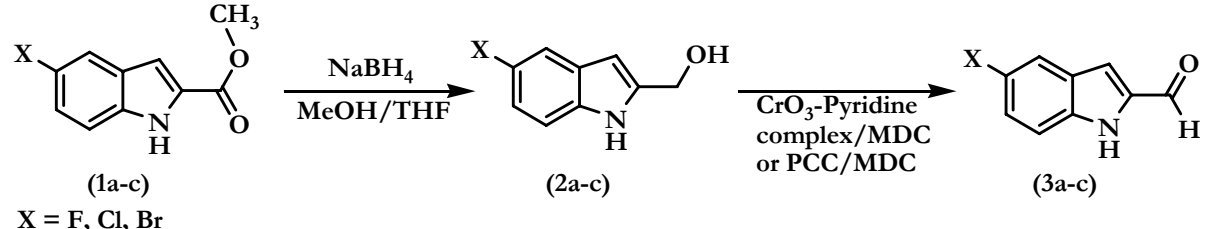
### General

Melting points were taken in open capillary tubes and are uncorrected. The purity of the compounds confirmed by thin layer chromatography using Merck silica gel 60 $F_{254}$ coated aluminium plates. IR spectra were recorded on Shimadzu-FTIR Infrared spectrometer in KBr ($\nu_{max}$ in $cm^{-1}$). $^1H$ NMR spectra were recorded in $CDCl_3$ and in DMSO-$d_6$ on a Varian (300 MHz) spectrometer using TMS as internal standard and $^{13}C$ NMR spectra were recorded in $CDCl_3$ and in DMSO-$d_6$ on a Varian (75 MHz) spectrometer. FABMS spectra were recorded on a JEOL SX 102/ DA-6000 mass spectrometer using argon/ xenon (6kv, 10mA) as the FAB gas.

### Synthesis of methyl 5-fluoro/chloro/bromoindole-2-carboxylate (1a-c)[11]

### Synthesis of methyl 5-fluoroindole-2-carboxylate (1a)

Methylpyruvate-4-fluorophenylhydrazone (2g, 0.0095mole) was taken in 10g polyphosphoric acid




(1a-c) (2a-c) (3a-c)

X = F, Cl, Br

SCHEME 1

**TABLE 1: The characterization data of compounds (1a-c), (2a-c) and (3a-c)**

| Compd. | Yield % | m.p. $^0$C | Spectral data |
|---|---|---|---|
| **1a** | 65 | 200-02 | $^1$H NMR ($CDCl_3$, 300MHz)- δ 3.92 (s, 3H, -$CH_3$), δ 7.01 (dt (*J*=8.7,2.4Hz, 1H, Ar-H), δ 7.10 (s, 1H,Ar-H), δ 7.26 (dd (*J*=9.3,2.1Hz), 1H,Ar-H), δ 7.44(dd (*J*=8.7,4.2 Hz), 1H, Ar-H), δ 9.39 (s, 1H,-NH-, exchangeable with $D_2O$); $^{13}$C-NMR($CDCl_3$+DMSO, 75MHz)- 51.36, 105.57 (d (*J*=24.0 Hz), 107.35 (d (*J*=4.5 Hz), 113.24 (d (*J*=27 Hz), 113.23,126.64 (d (*J*=11.25Hz), 128.46, 157.25 (d, *J*=233.2Hz),161.72 FT-IR (KBr): 3332.8 cm$^{-1}$ (-NH str.), 3284cm$^{-1}$ (-NH str.), 1701 cm$^{-1}$ (-C=O str.), 1153 cm$^{-1}$ (-C-O str.); *Anal.*Calcd. for $C_{10}H_8FNO_2$: C,62.18;H, 4.17; N,7.25; Found C,62.02 ; H, 4.04; N,7.16. |
| **1b** | 60 | 220-23 | $^1$H NMR ($CDCl_3$, 300MHz)- δ 3.92 (s, 3H, -$CH_3$), δ 7.07 (s,1H, Ar-H), δ 7.18 (d (*J*=8.7Hz,1H, Ar-H), δ 7.45 (d (*J*=8.7Hz), 1H, Ar-H), δ 7.61 (s, 1H, Ar-H) δ 11.78 (s, 1H,-NH-, exchangeable with $D_2O$); $^{13}$C NMR($CDCl_3$+DMSO, 75MHz)- 51.43, 106.83, 113.69, 120.65, 124.46,125.01, 127.49, 128.33,135.57,161.56; FT-IR (KBr): 3325 cm$^{-1}$ (-NH), 1699.2 cm$^{-1}$ (-C=O),1060cm$^{-1}$ (-C-O), 765cm$^{-1}$ (-C-Cl); *Anal.*Calcd. for $C_{10}H_8ClNO_2$: C,57.30;H, 3.87; N,6.68; Found C,57.1; H, 8.57; N,6.39. |
| **1c** | 65 | 208-10 | $^1$H NMR ($CDCl_3$, 300MHz)- δ 3.91 (s, 3H, -$CH_3$), δ 7.06 (s , 1H, Ar-H), δ 7.29 (d(*J*=10.2 Hz, 1H, Ar-H), δ 7.39 (d (*J*=8.7 Hz,1H,Ar-H), δ 7.75(s, 1H, Ar-H), δ 11.63 (s, 1H,-NH-, exchangeable with $D_2O$); $^{13}$C NMR ($CDCl_3$+DMSO, 75 MHz)- 51.44, 106.73, 112.73, 114, 123.84, 126.95, 128.13, 128.23, 135.76, 161.61; FT-IR (KBr): 3325 cm$^{-1}$ (-NH), 1697.2cm$^{-1}$ (-C=O); *Anal.*Calcd. for $C_{10}H_8BrNO_2$: C,47.27;H, 3.17; N,5.51; Found C,47.10 ; H, 5.31; N,5.28. |
| **2a** | 68 | 88-90 | $^1$H NMR :($CDCl_3$+DMSO-$d_6$, 300 MHz)- δ 2.21 (brs, 1H, -OH), δ 4.77 (s, 2H, -$CH_2$), δ 6.33 (s, 1H,Ar-H), δ 6.90 (dt (*J* =2.1 Hz, 1H, Ar-H), δ 7.18(d (*J* = 3.3Hz, 1H, Ar-H), δ 7.23 (d (*J* = 9.0 Hz, 1H, Ar-H), δ 8.45 (br s, 1H, -NH-, exchangeable with $D_2O$); $^{13}$C NMR ($CDCl_3$, 75MHz)- 58.58, 100.49, 100.33 (d, *J*=23.2Hz), 110.45 (d, *J*=25.5Hz), 111.48(d (*J*=9.75 Hz), 128.4(d, *J*=9.75Hz), 132.80, 139.28, 157.94(d, *J*=233Hz); FT-IR (KBr): 3338.6cm$^{-1}$ (-OH), 3284cm$^{-1}$ (-NH), 2922 cm$^{-1}$ (-$CH_2$), 1163 cm$^{-1}$ (-C-O); *Anal.*Calcd. for $C_9H_8FNO$: C,65.45;H, 4.88; N,8.48; Found C,65.24 ; H, 4.53; N,8.24. |
| **2b** | 65 | 115-17 | $^1$H NMR :($CDCl_3$+DMSO-$d_6$, 300 MHz)- δ 2.15 (brs, 1H, -OH), δ 4.78 (s, 2H, -$CH_2$), δ 6.31 (s, 1H,Ar-H), δ 7.17 (dd, *J*=8.4Hz, 2H, Ar-H), δ 7.52 (s,1H, Ar-H), δ 8.49 (br s, 1H, -NH-, exchangeable with $D_2O$); $^{13}$C NMR($CDCl_3$, 75MHz)- 58.54, 100.01, 111.89, 119.95, 122.40, 125.48, 129.18, 134.62, 138.93; FT-IR (KBr): 3400cm$^{-1}$ (-OH), 3344 cm$^{-1}$ (-NH), 2362 cm$^{-1}$ (-$CH_2$), 1139cm$^{-1}$ (-C-O); *Anal.*Calcd. for $C_9H_8ClNO$: C,59.52;H, 4.44; N,7.71; Found C,59.38 ; H, 4.23; N,7.54. |
| **2c** | 65 | 106-08 | $^1$H-NMR :($CDCl_3$+DMSO-$d_6$, 300 MHz)- δ 2.33 (brs, 1H, -OH), δ 4.74 (s, 2H, -$CH_2$), δ 6.28 (s, 1H,Ar-H), δ 7.11(dd, *J* =8.4Hz, 2H,Ar-H), δ 7.66 (s, 1H, Ar-H), δ 8.52 (br s, 1H, -NH-, exchangeable with $D_2O$); $^{13}$C-NMR($CDCl_3$, 75MHz)- 58.46, 99.90, 112.33, 112.99, 123.03, 124.92, 129.82, 134.89, 138.75; FT-IR (KBr): 3390 cm$^{-1}$ (-OH), 3242cm$^{-1}$ (-NH), 2935cm$^{-1}$ (-$CH_2$), 1139 cm$^{-1}$ (-C-O); *Anal.*Calcd. for $C_9H_8BrNO$: C,47.82;H, 3.57; N,6.20; Found C, 47.56; H, 3.35; N,6.02. |
| **3a** | 74 | 164-65 | $^1$H NMR :($CDCl_3$+DMSO-$d_6$, 300 MHz)- δ 7.08 (dt (d, *J*=2.1Hz, 1H, Ar-H), δ 7.20 (s, 1H, Ar-H), δ 7.34 (d, *J*=9.0Hz, 1H, Ar-H), δ 7.46(d, *J*=4.5.Hz, 1H, Ar-H), δ 9.84 (s, 1H,-CHO), δ 11.56 (br s, 1H, -NH-, exchangeable with $D_2O$); $^{13}$C NMR ($CDCl_3$, 75MHz)- 106.01 (d, *J*=23.25Hz), 113.1, 113.6 (d, *J*=9.0Hz), 114.9 (d, *J*=27 Hz), 126.3 (d, *J*=11.2Hz), 134.7, 136.96,157.17(d, *J*=234 Hz),181.6; FAB MS: m/z 163 (I=75%, M$^+$), 164 ( I=100%,M+1), 136 (I=55%,M-CHO); *Anal.*Calcd. for $C_9H_6FNO$: C, 66.26; H, 3.71; N, 8.59; Found C, 66.02 ; H, 3.71; N, 8.59. |
| **3b** | 82 | 204-06 | $^1$H NMR: ($CDCl_3$+DMSO-$d_6$, 300 MHz)- δ 7.21 ( s, 1H, Ar-H), δ 7.37 (dd, *J=8.7*, 2H, Ar-H), δ 7.73 (s, 1H, Ar-H), δ 9.13 (s, 1H, Ar-CHO), δ 9.85 (brs, 1H, -NH-, exchangeable with $D_2O$); FAB MS: m/z 179 (I=38%, M$^+$), 180 ( I=40%,M+1), 154 (I=100%, M+2-CHO); FT-IR (KBr): 1656cm$^{-1}$ (-CHO), 3298 (-NH-); *Anal.*Calcd. for $C_9H_6ClNO$: C, 60.19; H, 3.37; N, 7.80; Found C, 60.01; H, 3.10; N, 7.60. |
| **3c** | 76 | 178 | $^1$H NMR :($CDCl_3$+DMSO-$d_6$, 300 MHz)- δ 7.17 ( s, 1H, Ar-H), δ 7.40 (dd, *J*=8.7 Hz,2H, Ar-H), δ 7.84 (s, 1H, Ar-H), δ 9.87 (s, 1H, Ar-CHO), δ 11.69 (br s, 1H, -NH-, exchangeable with $D_2O$); $^{13}$C NMR ($CDCl_3$, 75MHz)- 112.59, 113.08, 113.31, 114.40, 122.92, 124.66, 126.68, 128.11, 128.74, 136.73, 136.82; FAB MS: m/z 224 (I=27%, M$^+$), 226( I=25%, M+1); FT-IR (KBr): 1658.7cm$^{-1}$ (-CHO), 3296.1 (-NH-); *Anal.*Calcd. for $C_9H_6BrNO$: C, 48.25; H, 2.70; N, 6.25; Found C, 48.06; H, 2.48; N, 6.12. |

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and kept under stirring for proper mixing. Slowly heated the reaction mass to 75-85$^0$C and maintain for 0.5h. Progress of the reaction was monitored by TLC. Cooled the reaction mass and added 100mL DM water to break the lumps till it becomes slurry. Filtered the solid separated and washed with 5% sodium bicarbonate solution followed by water. After one recrystallisation from ethyl acetate, Methyl-5-fluoroindole-2-carboxylate **(1a)** was obtained as off white crystals.

**Synthesis of methyl 5-chloroindole-2-carboxylate (1b)**

Prepared from methylpyruvate-4-chlorophenylhydrazone (2g, 0.0088mol) at 50-60$^0$C using poly phosphoric acid as described under methyl-5-fluoroindole-2-carboxylate **(1b)**. The product was obtained as cream crystals.

**Synthesis of methyl 5-bromoindole-2-carboxylate (1c)**

Prepared from methylpyruvate -4-bromophenylhydrazone (2g, 0.00738mol) at 55-65$^0$C using poly phosphoric acid as described for the preparation of methyl-5-fluoroindole-2-carboxylate **(1c)**. The product was obtained as cream crystals.

**General method for the synthesis of 5-fluoro/chloro/bromoindole-2-methanol (2a-c)**

Sodium borohydride (0.04mole) was added to respective methyl-5-fluoro/chloro/bromoindole -2-carboxylate (0.01mole) in 25mL THF. The mixture was heated to 65$^0$C and maintained for 15min. Methanol (3mL) was then carefully added dropwise during 30 minutes. During the addition effervescence was observed. Stirring was maintained for 2-3h at the same temperature. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, quenched with saturated aqueous ammonium chloride solution (20mL) and continued stirring for 1.5h. Reaction mixture was then extracted in ethyl acetate (2x25mL), dried over anhydrous sodium sulphate and concentrated to residue. The residue was then purified by flash chromatography. The compounds were further recrystallised in ethyl acetate. The compounds are isolated in 65-68% yield.

**General method for the oxidation of 5-fluoro/chloro/bromoindole-methanols to 5-fluoro/chloro/bromoindole-2-aldehydes (3a-c)**

**Method A: Oxidation with PCC (Pyridinium chlorochromate)**

To a stirred solution of PCC (0.014mole) in 40mL methylene dichloride, 5-fluoro/ chloro/ bromoindole -2-methanol (0.01mole) was added and stirred for 45 minutes at room temperature. Progress of the reaction was monitored by TLC. After the completion of the reaction, the clear solution was decanted and concentrated. The residue was then purified by passing through silica gel column with methylene dichloride as eluent. Products were isolated in 73-82% yield.

**Method B: Oxidation with chromium trioxide-pyridine complex**

Chromium trioxide (0.0146 mole) was added to 20mL of pyridine at 15- 20$^0$C and stirred for 15 minutes. 5-Chloro/bromoindole-2-methanol (0.01mole) in 5ml pyridine was then added slowly and brought to room temperature. Reaction mixture was stirred for 1h at room temperature. Progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was cooled and poured in to water. The mixture was filtered through hyflo and extracted with 75mL methylene dichloride. The organic layer was then concentrated and the residue was purified by column chromatography. 5-Fluoroindole-2-carboxaldehyde was prepared by carrying out the reaction as described for 5-chloro/bromoindole-2-carboxaldehyde, but temperature maintenance at 65-75°C. Products were isolated in 75-82 % yield.

## CONCLUSION

We report a simple and cost effective method for the reduction of methyl 5-fluoro/chloro/bromoindole-2-carboxylate to 5-fluoro/chloro/bromoindole -2-methanol with sodium borohydride in methanol/tetrahydrofuran media. All the compounds are isolated in good yield and purity. We also report an efficient, simple and cost effective method for the further oxidation of 5-fluoro/ chloro/ bromoindole -2-methanols to 5-fluoro/ chloro/

bromoindole-2-aldehydes with PCC and chromium trioxide-pyridine complex prepared *in situ*. Both methods resulted in good yields and purity and are viable for large-scale preparation of 5-fluoro/ chloro/bromoindole -2-aldehydes.

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