Synthesis of 4-, 5-, 6- and 7-nitroindole-2-methanols and 4-, 5-, 6- and 7-nitroindole-2-carbaldehydes

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The synthesis of 4-, 5-, 6- and 7-nitroindole-2-methanols and the corresponding 2-aldehydes is described. The nitroindole-2-methanols were prepared by the reduction of ethyl 4-, 5-, 6- and 7-nitroindole-2-carboxylates with sodium borohydride in methanol/tetrahydrofuran. 4-, 5-, 6- and 7-Nitroindole-2-aldehydes were prepared from the nitroindole-2-methanols using PCC (pyridinium chlorochromate) and with chromium trioxide–pyridine prepared *in situ*.

Keywords: nitroindoles, methanols, aldehydes

The indole nucleus is a structural unit found in many natural products and many biologically active molecules.[1] The synthesis of indole-2-methanol is reported using lithium aluminium hydride[2,3] and, less known in the literature, using sodium borohydride. Since its discovery by Brown and co-workers,[4] sodium borohydride has become widely used in reduction processes for a range of functional groups.[5] The reduction of aromatic esters to alcohols can be conveniently carried out in good yield using sodium borohydride.[6,7]

The synthesis of nitroindole-3-aldehydes is much discussed,[8] but less is known of the synthesis of nitroindole-2-aldehydes. The preparation of indole-2-carbaldehydes has been reported from indole-2-methanols in 50–68 % yield by oxidation with MnO_2.[9,10] Indole-2-aldehydes are also prepared by McFadyen-Stevens reduction of the corresponding indole-2-carboxylic acid derivatives.[11] They are also prepared by the reduction of corresponding acid chloride using lithium tri-*t*-butoxyaluminium hydride, which is prepared from $LiAlH_4$ and *t*-butanol.[12] Indole-2-carbaldehyde is also prepared from the corresponding alcohol using silver(I) carbonate.[13] Photo-oxidation of methylindoles to indole-2- and -3-carbaldehyde has also been reported in the literature.[14]

Chromic acid in a variety of acidic media, has been used extensively for the oxidation of primary alcohols to aldehydes but rarely has provided aldehydes in greater than 50 % yield.[15] Chromium trioxide-pyridine was introduced as a unique, non-acidic reagent for alcohol oxidations and has been used extensively to prepare ketones[16] but rarely for aldehydes. Collins and co-workers[17] found that anhydrous dipyridine-chromium(VI) oxide is moderately soluble in chlorinated hydrocarbons and recommended dichloromethane as solvent. With this modification, primary and secondary alcohols were oxidised 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(VI) oxide, its hygroscopic nature, and its propensity to catch fire during preparation.[18,19] The preparation of chromium trioxide-pyridine complex *in situ* avoids these difficulties.[20]

Various other reagents for the oxidation of primary alcohols to aldehydes under mild and non-aqueous conditions have been developed. Pyridinium chlorochromate, pyridinium dichromate and chromium trioxide –3,5-dimethylpyrazole complex have been reported to be effective reagents for the oxidation of primary alcohols to aldehydes in aprotic solvents.[21] Among the above mentioned reagents, pyridinium chlorochromate is proved to be most popular because it can easily be prepared and stored, it allows the efficient oxidation of a variety of alcohols using only a modest excess of oxidant, and may be amenable to large scale operations.

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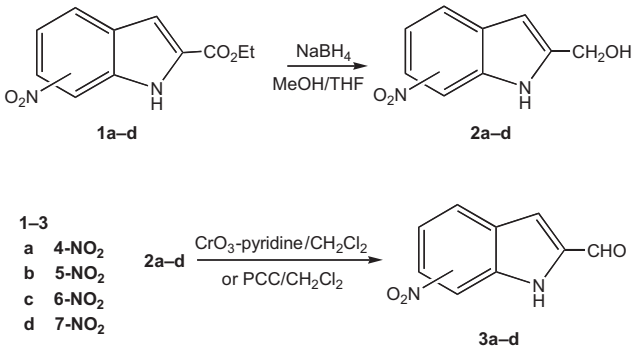

Scheme 1

In consideration of the above, we planned the reduction of ethyl esters of nitroindole-2-carboxylic acids to the corresponding nitroindole-2-methanols using sodium borohydride and methanol (Scheme 1). This methodology is simple and inexpensive, and the selective reduction of esters was completed after 4 h reflux in THF. The respective alcohol products were isolated after workup in fair yields (56–65 %) without affecting the reduction of the nitro group. All the compounds are characterised by spectral and elemental analysis.

We also developed a facile and efficient method for the oxidation of 4-, 5-, 6- and 7-nitroindole-2-methanols to the corresponding 2-aldehydes with PCC (pyridinium chlorochromate) and also with chromium trioxide–pyridine complex prepared *in situ* (Scheme 1). The present method is very simple, and superior to the others reported for the oxidation of indole-2-methanols.[9-11] All the compounds are characterised by spectral and elemental analysis. Both PCC and chromium trioxide–pyridine complex gave comparable results with respect to reaction time and yield. With PCC the reaction was complete in 45 minutes at room temperature, whereas with chromium trioxide–pyridine system the reaction took 60 minutes to complete at 80 °C. The yields obtained with PCC are comparable with those using the chromium trioxide–pyridine system. Both of the methods are viable for the large-scale preparation of nitroindole-2-carbaldehydes.

Experimental

Melting points were taken in open capillary tubes. The purity of the compounds was confirmed by thin layer chromatography using Merck silica gel 60 F_{254} coated aluminium plates. IR spectra were recorded on Shimadzu-FT IR spectrometre in KBr (ν_{max} in cm^{-1}). ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$/DMSO-d_6 mixture, unless otherwise stated, on a Varian 300 MHz spectrometre using TMS as internal standard. FAB MS spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometre using argon/xenon (6kV, 10 mA) as the FAB gas.

4-,5-,6- and 7-Nitroindole-2-methanol

Sodium borohydride (1.87 g, 0.046 mol) was added to the appropriate ethyl nitroindole-2-carboxylate[22] (2.34 g, 0.01 mol) in THF (25 ml). The mixture was heated to 65 °C and the temperature maintained for 15 min. Methanol (3 ml) was then slowly added dropwise over 30 min. During the addition effervescence was observed. Stirring was continued for 4 h at the same temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature, quenched with saturated aqueous ammonium chloride (20 ml), and continued stirring for 1.5 h. The reaction product was then extracted into ethyl acetate (2 × 50 ml), dried over anhydrous sodium sulfate, and the solvent was removed *in vacuo*. The residue was then purified by flash chromatography with dichloromethane/ethyl acetate as eluent. The products were recrystallised from ethyl acetate.

4-Nitroindole-2-methanol (**2a**): Yellowish-orange crystals, yield 62 %, m.p. 171–173 °C. IR: 3367 (OH), 3284 (NH), 2922 (CH_2), 1504, 1321 (NO_2), 1068 cm^{-1} (C–O). ^1H NMR: δ 2.45 (brs, 1H, OH), 4.85 (s, 2H, CH_2), 7.08 (s, 1H, Ar–H), 7.18 (t, 1H, Ar–H), 7.68 (d, *J* = 7.8 Hz, 1H, Ar–H), 8.07 (d, *J* = 8.1 Hz, 1H, Ar–H), 10.53 (br s, 1H, NH, exchangeable with D_2O). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 57.7, 99.4, 117.0, 117.8, 119.7, 122.4, 138.4, 139.5, 144.4. Anal. Calc. for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58. Found: C, 56.20; H, 4.22; N, 14.48 %.

5-Nitroindole-2-methanol (**2b**): Light brown crystals, yield 65 %, m.p. 152–154 °C (Lit[3c] 156–157 °C). ^1H NMR: δ 4.38 (brs, 1H, OH), 4.79 (s, 2H, CH_2), 6.50 (s, 1H, Ar–H), 7.38 (d,,*J* = 9.0 Hz, 1H, Ar–H), 8.02 (dd, 1H, *J* = 2.1, 9.3 Hz, Ar–H), 8.49 (d, 1H, *J* = 1.8 Hz,Ar–H), 10.41 (br s, 1H, NH,exchangeable with D_2O). ^{13}C NMR ($CDCl_3$) δ 57.6, 101.2, 110.7, 116.9, 117.2, 127.3, 139.4, 141.2, 142.6. MS: *m/z* 191 (M-1, 45 %), 193 (M + 1, 47 %), 160 (M-CH_3OH, 54 %). IR (KBr): 3360 (OH), 3290 (NH), 2933 (CH_2), 1512, 1326 (NO_2), 1068 cm^{-1} (C–O). Anal. Found: C, 56.24; H, 4.18; N, 14.56 %.

6-Nitroindole-2-methanol (**2c**): Light brown crystals, yield 60 %, m.p. 175–176 °C. IR: 3438 (OH), 3174 (NH), 2677 (CH_2), 1544, 1300 (NO_2), 1068 cm^{-1} (C–O). ^1H NMR: δ 4.79 (s, 2H, CH_2), 5.09 (t, 1H, OH), 6.43 (s, 1H, Ar–H), δ 7.54 (d, *J* = 8.7 Hz, 1H, Ar–H), δ 7.90 (d, *J* = 10.5 Hz, 1H, Ar–H), 8.32 (s, 1H, Ar–H), 11.20 (br s, 1H, NH, exchangeable with D_2O). ^{13}C NMR ($CDCl_3$): δ 57.0, 98.9, 107.4, 113.9, 118.85, 132.7, 134.1, 141.3, 146.0. Anal: Found: C, 56.24; H, 4.18; N, 14.54 %.

7-Nitroindole-2-methanol (**2d**): Brown crystals, yield 56 %, m.p. 130–132 °C**.** IR: 3413 (OH), 3352 (NH), 2677 (CH_2), 1544, 1300 (NO_2), 1068 cm^{-1} (C–O). ^1H NMR: δ 3.94 (s, 2H, CH_2), 4.89 (s, 1H, OH), 6.65 (d, *J* = 7.2 Hz, 1H, Ar–H), 6.96 (d, *J* = 7.5 Hz, 1H, Ar–H), 6.86 (t, 1H, Ar–H), 7.0 (s, 1H, Ar–H), 9.83 (br s, 1H, NH, exchangeable with D_2O). ^{13}C NMR ($CDCl_3$): 58.2, 101.4, 109.8, 110.1, 113.5, 119.1, 126.5, 128.4,131.9,163.3; MS: *m/z* 191 (M–1, 40 %), 192.1 (M^+, 5 %), 159.1 (M-CH_3OH, 54 %). Anal. Found: C, 56.19; H, 4.20; N, 14.54 %.

Oxidation of 4-,5-,6- and 7-nitroindole-2-methanol to 4-,5-,6- and 7-nitroindole-2-carbaldehyde

Method A: Oxidation with PCC (pyridinium chlorochromate.). Preparation of PCC: chromium trioxide (10 g, 0.1 mol) was slowly added to a mixture of 4 ml water and 12.5 ml conc. hydrochloric acid at room temperature. The mixture was then cooled to 0 °C and pyridine (7.9 g) was very slowly added. To the resulting solution a mixture of ethyl acetate (10 ml) and hexane (40 ml) was added and the whole was stirred for 30 min. The solid obtained was filtered and sucked dry. Yield 23.8 g (87 %). This reagent is used for the reaction.

Procedure: To a stirred solution of PCC (3.01 g, 0.014 mole) in methylene dichloride (40 ml), nitroindole-2-methanol (1.92 g, 0.01 mole) was added and the mixture was stirred for 45 minutes at room temperature. Progress of the reaction was monitored by TLC. After completion of the reaction the clear solution was decanted and concentrated. The residue was purified on a silica gel column with methylene dichloride as eluent. All the four products were isolated in 84–86 % yield. and were further recrystallised in ethanol.

Method B: Oxidation with chromium trioxide-pyridine complex: Chromium trioxide (1.46 g, 0.0146 mole) was added to pyridine (30 ml) at 15–20 °C. After stirring for 15 minutes nitroindole-2-methanol (1.92 g) in pyridine (5 ml) was added slowly and the mixture was heated to 80 °C. Reaction mixture was maintained at 80 °C for 1 h. The progress of the reaction was monitored by TLC. After completion of the reaction the mixture was cooled and poured into water. The mixture was filtered through hyflo and extracted with dichloromethane (75 ml). The organic layer was concentrated and the residue was purified by column chromatography. All the four products were isolated in 75–82 % yield and were recrystallised from ethanol.

4-Nitroindole-2-carbaldehyde (**3a**): Yellow crystals, m.p. 212–214 °C. IR: 1664 (CHO), 3294 cm^{-1} (NH).^1H NMR: δ 7.43 (t, 1H, Ar–H), 7.8 (s, 1H, Ar–H), 7.89 (d, *J* = 9.0 Hz, 1H, Ar–H), 8.12 (d, *J* = 9.0 Hz, 1H, Ar–H), 7.68 (d, *J* = 7.8 Hz, 1H, Ar–H), 9.97 (s, 1H, CHO), 12.39 (br s, 1H, NH, exchangeable with D_2O). ^{13}C NMR ($CDCl_3$): δ 111.7, 117.4, 119.5, 119.8, 123.8, 137.7, 139.1, 140.7, 181.8. FAB MS: *m/z* 191 (M + 1, 45 %), *m/z* 214 ((M + 1) + Na, 55 %), *m/z* 228 ((M-1 + K), 54 %). Anal. Calc. for $C_9H_6N_2O_3$: C, 56.85; H, 3.18; N, 14.73. Found: C, 56.83; H, 3.20; N, 14**.**74 %.

5-Nitroindole-2-carbaldehyde (**3b**): Brownish yellow crystals, m.p. 238–242 °C (Lit.[14] 246-247 °C); IR: 1658 (CHO), 3251 cm^{-1} (NH). ^1H NMR: δ 7.45 (s, 1H, Ar–H), δ 7.58 (d, *J* = 9.3 Hz, 1H, Ar–H), 8.15 (dd, *J* = 2.1, 9.0 Hz, 1H, Ar–H), 8.7 (d, *J* = 2.1 Hz, 1H, Ar–H), 9.93 (s, 1H, CHO), 12.37 (br s, 1H, NH, exchangeable with D_2O). ^{13}C NMR ($CDCl_3$): 113.1, 115.1, 119.9, 120.4, 125.6, 138.6, 140.8,141.7, 182.0. FAB MS: *m/z* 191 (M + 1, 48 %), 214 ((M + 1 + Na) 62 %), *m/z* 228 ((M-1 + K) 54 %). Anal. Found: C, 56.84; H, 3.19; N, 14.74 %.

6-Nitroindole-2-aldehyde (**3c**): Yellow powder, m.p. 230–232 °C. IR: 1659 (CHO), 3310 cm^{-1} (NH). ^1H NMR: δ 7.32 (s, 1H, Ar–H), 7.83 (d, *J* = 8.7 Hz, 1H, Ar–H), 7.95 (d, *J* = 8.7 Hz, 1H, Ar–H), 8.45 (s, 1H, Ar–H), 9.95 (s, 1H, CHO), 12.35 (br s, 1H, NH, exchangeable with D_2O). ^{13}C NMR ($CDCl_3$): δ 109.5, 112.3, 114.5, 122.8, 130.6, 136.4, 139.6, 145.3, 182.0. FAB MS: *m/z* 191(M + 1, 55 %), 214 ((M + 1) + Na, 58 %). Anal. Found: C, 56.82; H, 3.16; N, 14.74 %.

7-Nitroindole-2-aldehyde (**3d**): Yellow powder, m.p. 163–165 °C. IR (KBr): 1678 (CHO), 3274 cm^{-1} (NH). ^1H NMR: δ 7.36 (t, 1H, Ar–H), 7.44 (s, 1H, Ar–H), 8.14 (d, *J* = 8.1 Hz, 1H, Ar–H), 8.35 (d, *J* = 8.1 Hz, 1H, Ar–H), 9.99 (s, 1H, CHO), 10.65 (br s, 1H, NH, exchangeable with D_2O); ^{13}C NMR ($CDCl_3$): 133.6, 120.2, 123.3, 130.4, 130.5, 131.3, 137.4, 181.6. FAB MS: *m/z* 191(M + 1, 60 %). Anal. Found: C, 56.82; H, 3.16; N, 14.72 %.

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