Synthesis of functionalised indoline spiropyrans by condensation of indolo[2,1-*b*][1,3]benzoxazines with *ortho*-hydroxy-substituted aromatic aldehydes

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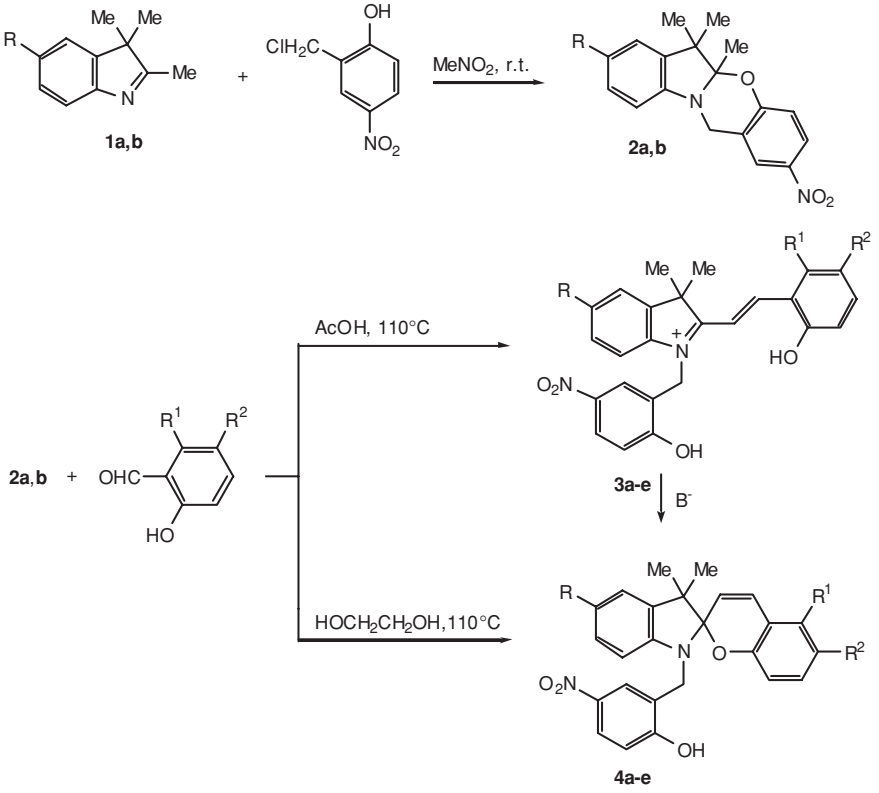
Condensation of 5a,6-dihydro-5a,6,6-trimethyl-2-nitro-12*H*-indolo[2,1-*b*][1,3]benzoxazine derivatives with *ortho*-hydroxy-substituted aromatic aldehydes afforded 1'-(2-hydroxy-5-nitrobenzyl)spiro[1-benzopyran-2,2'-indoline].

Keywords: indolo[2,1-*b*][1,3]benzoxazine, salicylaldehyde, condensation, indoline spiropyran

Indoline spiropyrans are heterocyclic compounds which have been studied extensively due to their potential applications in organic functional materials.[1] The main method for their synthesis is based on condensation of 1,2,3,3-tetrasubstituted-3*H*-indolium salts or the corresponding 2-alkylidene indolines, the Fischer's bases, with *ortho*-hydroxy-substituted aromatic aldehydes.[2] The Fischer's bases are usually prepared by *N*-alkylation of indolenines with alkyl halides, sulfates, *p*-toluenesulfonates or other similar alkylating agents, and treatment of the formed *N*-substituted 3*H*-indolium salts with base.[3] Reaction of the corresponding indolenines with such bifunctional alkylating agent as 2-bromoethanol or ethylene oxide produced indolo[1,2-*b*]oxazole derivatives,[4] while their alkylation with 2-chloromethyl-4-nitrophenol led to the formation of indolo[2,1-*b*][1,3]benzoxazine derivatives.[5] Indolo[1,2-*b*]oxazoles found a number of applications as starting materials for preparation of various commercially important organic compounds, including methine dyes,[6] electrochromic styryls[7] and photochromic spiropyrans.[8] However, the potential utilisation of indolo[2,1-*b*][1,3] benzoxazine derivatives for similar synthetic purposes has not been investigated yet.

This study is focused on the synthesis of new functionalised indoline spiropyrans by condensation of 5a,6-dihydro-12*H*-indolo[2,1-*b*][1,3]benzoxazine derivatives with *ortho*-hydroxy-substituted aromatic aldehydes. The starting 5a,6-dihydro-12*H*-indolo[2,1-*b*][1,3]benzoxazines **2a,b** were synthesised by reacting of 2,3,3-trimethyl-3*H*-indoles **1a,b** with 2-chloromethyl-4-nitrophenol in nitromethane (Scheme 1).

Condensation of compounds **2a**,**b** with salicylaldehyde, 5-nitrosalicylaldehyde or 2-hydroxy-1-naphthaldehyde in acetic acid produced coloured solutions of 2-styryl-3*H*-



1, **2a** R = H; **b** R = Br; **3, 4a** R = R^1 = R^2 =H; **b** R = R^1 = H, R^2 = NO_2; **c** R = H, R^1 + R^2 = CH=CH-CH=CH; **d** R = Br, R^1 = R^2 =H; **e** R = Br, R^1 + R^2 = CH=CH-CH=CH

Scheme 1

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indolium acetates **3a**–**e**. It can be suggested that in an acidic medium the oxazine ring of the starting 5a,6-dihydro-12*H*-indolo[2,1-*b*][1,3]benzoxazines opens and formation of the corresponding 1-(2-hydroxy-5-nitrobenzyl)-3*H*-indolium salts takes place. Subsequent condensation of the active 2-methyl group of the 3*H*-indolium cation and the formyl group of an aromatic aldehyde produces coloured styryl adducts. For example, the UV spectra of the solutions of the salts **3a**,**c**,**e** in acetic acid exhibited λ_{max} at 444, 506 and 518 nm, respectively. After treating the obtained solutions of **3a**–**e** with sodium acetate, followed by extraction and chromatographic purification, spiropyrans **4a**–**e** were crystallised as slightly yellowish substances in isolated yields of 19–35%.

However, when compounds **2a,b** were condensed with 2-hydroxy-1-naphthaldehyde in ethylene glycol at 110°C, using piperidine as a basic catalyst, the direct formation spiropyrans **4c,e** occurred in yields of about 50%. The same trend was followed, when **2a** and the aldehyde were mixed and heated in ethylene glycol without piperidine. Ethanol was not suitable for such condensation: after 24 h reflux most of the mixture remained unreacted.

The structures of compounds **4a–e** were confirmed by the data of IR, ^{1}H and ^{13}C NMR spectra and elemental analysis. For example, the ^{1}H NMR spectrum of compound **4a** demonstrates a doublet of the methine proton at 5.79 ppm with $^3J_{3,4}$ 10.0 Hz, indicating the *cis*-allocation of the vinylic protons in the spiropyran molecule[9], while the ^{13}C NMR spectrum exibits a signal of the spiro C-2 at 109.60 ppm. In the IR spectrum of **4a**, a band at 3328 cm^{-1} corresponds to O–H stretching vibrations, and those at 1519 and 1322 cm^{-1}, can be assigned to a nitro group.

In conclusion, 5a,6-dihydro-12*H*-indolo[2,1-*b*][1,3]benzoxazine derivatives can serve as versatile starting compounds for the preparation of functionalised indoline spiropyrans. Condensation of 5a,6-dihydro-12*H*-indolo[2,1-*b*][1,3] benzoxazine derivatives with *ortho*-hydroxy-substituted aromatic aldehydes can be easily performed in acetic acid or ethylene glycol.

Experimental

All melting points were determined with Kleinfeld melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded with TESLA BS 487 C (80 MHz) and Bruker Avance DPX-250 instrument (250 MHz). ^{13}C NMR spectra were obtained on a Bruker Avance DPX-250 instrument (62.5 MHz). Chemical shifts, expressed in ppm, were relative to tetramethylsilane (TMS). IR spectra were recorded on a Perkin Elmer Spectrum BXII spectrometer (KBr pellets). Mass spectra were recorded on a Hitachi M-80A instrument at ionising voltage 20eV. The UV spectra were determined with a Spectronic Genesys 8 spectrophotometer: λ_{max} in nm (logε). For thin layer chromatographic (TLC) analyses, precoated TLC plates (silica gel 60 F254, Merck) were used. Separations by column chromatography were performed on silica gel Merck, 9385, 230-400 mesh.

Compound **2a** was prepared following the previously reported procedure.[5]

8-Bromo-5a,6-dihydro-5a,6,6-trimethyl-2-nitro-12H-indolo[2,1-b][1,3]benzoxazine (**2b**): A solution of 2-chloromethyl-4-nitrophenol (7.50 g, 40 mmol) in 10 ml of nitromethane was added to a solution of 5-bromo-2,3,3-trimethyl-3*H*-indole (9.53 g, 40 mmol) in 10 ml of nitromethane. The mixture was stirred for 24 h at room temperature and the separated crystalline product (about 1.20 g) filtered off. The filtrate was poured into 120 ml of water, the solution treated with a concentrated solution of sodium acetate until alkaline, and extracted with diethyl ether (3 × 20 ml). The organic extract was washed with water (20 ml), the solution concentrated under reduced pressure, and the residue kept for 24h at 0°C. The precipitated yellowish crystals were separated, washed with ether (5 ml), and the combined crystalline material was recrystallised from ethanol to yield 8.56 g (55%) of **2b** with m.p. 197–198°C. MS *m/z* (rel. intensity): 390 (82, M^+, ^{81}Br), 388 (100, M^+, ^{79}Br); IR (KBr): 1509; 1338 (NO_2) cm^{-1}; ^{1}H NMR (80 MHz, CCl_4): δ 1.08 (3H, s, CH_3); 1.40 (3H, s, CH_3); 1.50 (3H, s, CH_3); 4.50 (2H, s, CH_2); 7.01–7.89 (6H, m, ArH) ppm. Calcd. for $C_{18}H_{17}BrN_2O_3$: C, 55.54; H, 4.40; Br, 20.53%. Found: C, 55.30; H, 4.57; Br, 20.87%.

1',3'-Dihydro-1'-(2-hydroxy-5-nitrobenzyl)-3',3'-dimethylspiro[1-benzopyran-2,2'-indole] (**4a**): A mixture of compound **2a** (0.62 g, 2.0 mmol) and salicylaldehyde (0.24 g, 2.0 mmol) in acetic acid (5 ml) was heated at 110°C for 5 h; then the mixture was poured into 5% sodium acetate (50 ml) and extracted with ether (2 × 15 ml). The combined organic layers were washed with water (10 ml), dried over Na_2SO_4, the solvent was evaporated *in vacuo* and the residue was chromatographed on a silica gel column with acetone-hexane 1:3 as eluent to afford 0.29 g (35%) of **4a** with m.p. 179–180°C (acetone). UV (EtOH): λ_{max} 250 (logε 4.06), 270 (3.96), 300 (4.03) nm; ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.26 (3H, s, CH_3); 1.29 (3H, s, CH_3); 4.16–4.38 (2H, AB-system, J = 17.5 Hz, CH_2); 5.79 (1H, d, J = 10.0 Hz, C*H*=CH); 6.21–8.07 (12H, m, ArH and CH=C*H*); 11.54 (1H, broad s, OH) ppm; ^{13}C NMR (DMSO-d_6): δ 22.65 (CH_3); 28.89 (CH_3); 44.57 (CH_2); 54.87 (C-indole); 107.30; 109.60 (C-O); 117.41; 118.03; 121.24; 121.74; 122.34; 123.36; 124.72; 125.77; 127.32; 129.04; 129.98; 130.47; 132.78; 132.86; 139.23; 142.69; 149.60; 156.48; 164.04 ppm. Calcd. for $C_{25}H_{22}N_2O_4$: C, 72.45; H, 5.35; N, 6.76%. Found: C, 72.35; H, 5.62; N, 6.83%.

1',3'-Dihydro-1'-(2-hydroxy-5-nitrobenzyl)-3',3'-dimethyl-6-nitrospiro[1-benzopyran-2,2'-indole] (**4b**) was obtained similarly to **4a** from **2a** (0.62 g, 2.0 mmol) and 5-nitrosalicylaldehyde (0.33 g, 2.0 mmol) in 0.26 g yield (28%) with m.p. 114–115°C (acetone). UV (EtOH): λ_{max} 250 (logε 4.08), 336 (4.05) nm; IR (KBr): 3378 (O–H), 1651 (CH=CH), 1511; 1335 (NO_2) cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.27 (3H, s, CH_3); 1.29 (3H, s, CH_3); 4.22–4.39 (2H, AB-system, J = 17.5 Hz, CH_2); 6.03 (1H, d, J = 10.5 Hz, C*H*=CH); 6.32–8.20 (11H, m, ArH and CH=C*H*), 11.48 (1H, broad s, OH) ppm; ^{13}C NMR (DMSO-d_6): δ 17.91 (CH_3); 24.43 (CH_3); 39.90 (CH_2); 50.85 (C-indole); 104.82; 105.40 (C-O); 113.58; 113.88; 117.08; 118.27; 119.43; 120.32; 121.30; 121.50; 122.93; 124.05; 124.21; 126.17; 127.13; 134.22; 138.13; 139.06; 144.74; 157.33; 159.57 ppm. Calcd. for $C_{25}H_{21}N_3O_6$: C, 65.35; H, 4.61; N, 9.15%. Found: C, 65.47; H, 4.71; N, 8.99%.

1,3-Dihydro-1-(2-hydroxy-5-nitrobenzyl)-3,3-dimethylspiro[indole-2,3'-naphtho[2,1-b]pyran] (**4c**): *Method A*. The reaction of compound **2a** (0.62 g, 2.0 mmol) with 2-hydroxy-1-naphthaldehyde (0.34 g, 2.0 mmol) and purification of the crude product was carried out analogously to the synthesis of compound **4a**. Yield of **4c** was 0.18 g (19%), m.p. 202–203°C (acetone). UV (EtOH): λ_{max} 252 (logε 4.16), 302 (4.10) nm; IR (KBr): 3423 (O–H), 1644 (C=C), 1513; 1338 (NO_2) cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.18 (3H, s, CH_3); 1.20 (3H, s, CH_3); 4.04–4.27 (2H, AB-system, J = 17.3 Hz, CH_2); 5.77 (d, J = 10.5 Hz, C*H*=CH); 6.10–8.05 (14H, m, ArH and CH=C*H*); 11.40 (1H, broad s, OH) ppm. Calcd. for $C_{29}H_{24}N_2O_4$: C, 74.98; H, 5.21; N, 6.03%. Found: C, 75.04; H, 5.26; N, 5.83%.

Method B. To a solution of compound **2a** (0.62 g, 2.0 mmol) and 2-hydroxy-1-naphthaldehyde (0.34 g, 2.0 mmol) in ethylene glycol (15 ml) two drops of piperidine were added and the mixture heated at 110°C for 4 h; then the mixture was poured into water (50 ml) and extracted with ether (2 × 15 ml). The combined organic layers were washed with water (10 ml), dried over Na_2SO_4, the solvent evaporated *in vacuo* and the residue crystallised from acetone to afford 0.45 g (48%) of compound **4c**, with m.p. and ^{1}H NMR spectrum identical to that of a sample obtained by the Method A.

Method C. Condensation of compound **2a** with 2-hydroxy-1-naphthaldehyde and work-up of the reaction mixture was performed analogously as described above (Method B). However, piperidine was not added to the starting reaction mixture. Yield of **4c** 45%.

5'-Bromo-1',3'-dihydro-1'-(2-hydroxy-5-nitrobenzyl)-3',3'-dimethylspiro[1-benzopyran-2,2'-indole] (**4d**) was obtained similarly to **4a** from **2b** (0.78 g, 2.0 mmol) and salicylaldehyde (0.24 g, 2.0 mmol) in 0.22 g yield (22%) with m.p. 195–196°C (acetone). UV (EtOH): λ_{max} 258 (logε 4.07), 298 (4.04) nm; IR (KBr): 3341 (O–H), 1642 (CH=CH), 1514, 1341 (NO_2) cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.16 (3H, s, CH_3); 1.18 (3H, s, CH_3); 4.14–4.35 (2H, AB-system, J = 17.5 Hz, CH_2); 5.68 (1H, d, J = 10.0 Hz, C*H*=CH); 6.08–7.96 (11H, m, ArH and CH=C*H*), 11.35 (1H, broad s, OH) ppm. Calcd. for $C_{25}H_{21}BrN_2O_4$: C, 60.86; H, 4.29; Br 16.20%. Found: C, 60.54; H, 4.23; Br, 16.35%.

5-Bromo-1,3-dihydro-1-(2-hydroxy-5-nitrobenzyl)-3,3-dimethylspiro[indole-2,3'-naphtho[2,1-b]pyran] (**4e**) was obtained similarly to **4c** from **2b** (0.78 g, 2.0 mmol) and 2-hydroxy-1-naphthaldehyde (0.34 g, 2.0 mmol) by the Methods A or B in yields 0.25 g (23%) and 0.59 g (54%), respectively; m.p. 161–162°C (acetone). UV (EtOH): λ_{max} 256 (logε 4.08), 296 (4.06) nm; IR (KBr): 3411 (O–H), 1640 (CH=CH), 1521, 1338 (NO_2) cm^{-1}; ^{1}H NMR (250 MHz, DMSO-d_6):

δ 1.32 (6H, s, 2 × CH_3); 4.19–4.42 (2H, AB-system, *J* = 17.7 Hz, CH_2); 5.89 (d, *J* = 10.5 Hz, C*H*=CH); 6.22–8.17 (13H, m, ArH and CH=C*H*); 11.54 (1H, broad s, OH) ppm. Calcd. for $C_{29}H_{23}BrN_2O_4$: C, 64.10; H, 4.27; Br, 14.70%. Found: C, 64.02; H, 4.56; Br, 14.54%.

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