A new synthetic approach towards 7-substituted 2-alkyl-2,3,4,9-tetrahydro-1*H*-fluorenes

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Cyclization of 2-(4-bromophenyl)-5-pentylcyclohex-1-ene-1-carboxylic acid followed by reduction of the carbonyl group resulted in the corresponding 7-substituted derivative of 2-alkyl-2,3,4,9-tetrahydro-1*H*-fluorene.

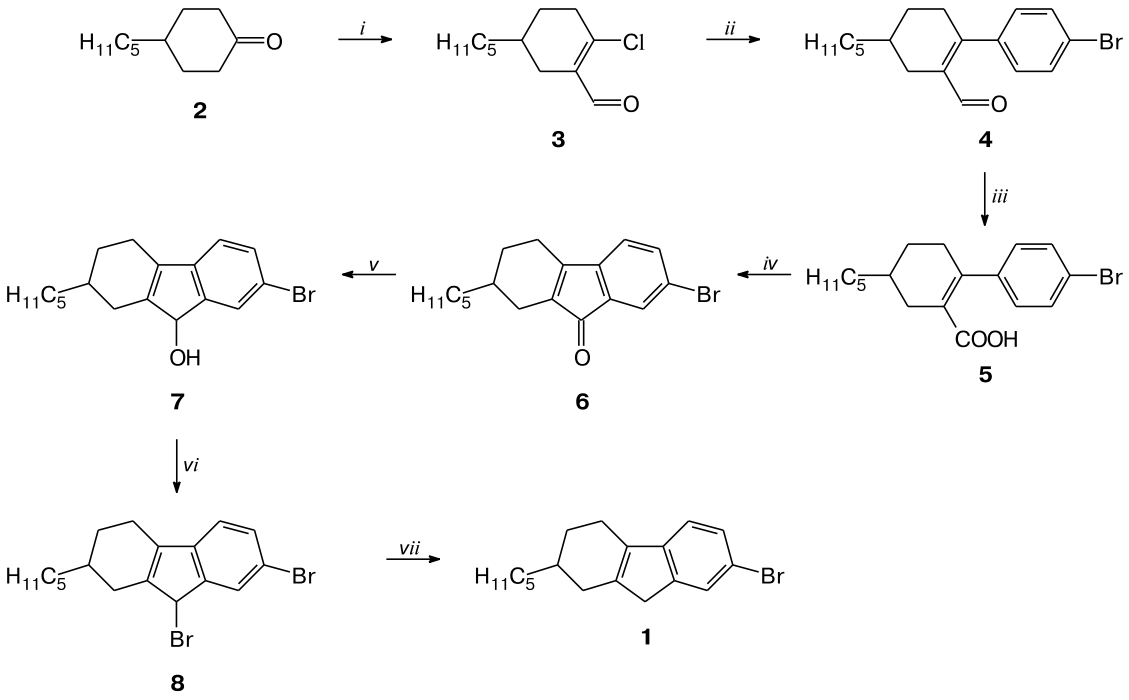
Key words: β-chloroenal, fluorenes, cross-coupling

In continuation of our study[1—3] in the field of liquid crystal structures bearing mono-, bi-, and tricyclic fragments, we developed a synthetic route towards key intermediates for preparing the novel class of liquid crystals, 7-substituted derivatives of 2-alkyl-2,3,4,9-tetrahydro-1*H*-fluorene.[4]

In the present work, we report synthetic approach towards hitherto unknown 7-bromo-2-pentyl-2,3,4,9-tetrahydro-1*H*-fluorene (**1**) (Scheme 1).

Formylation of 4-pentylcyclohexanone (**2**) with a mixture of phosphorus oxychloride and DMF in chloroform according to the Vilsmeier—Haack—Arnold procedure[5]

Scheme 1



i. 1) $POCl_3$, $HC(O)NMe_2$, $CHCl_3$, 5–10 °C, 10 min, 2) **1**, 50—60 °C, 3 h; *ii*. 4-$BrC_6H_4B(OH)_2$, BuNBr, 10% Pd/C, K_2CO_3, H_2O, 85 °C, 6 h; *iii*. $NaClO_2$, H_2O, 10—20 °C, 12 h; *iv*. 1) $SOCl_2$, DMF, CH_2Cl_2, 20 °C, 1 h, 2) reflux, 15 min, 3) $AlCl_3$, CH_2Cl_2, 20 °C, 30 min or $(CF_3CO)_2O$, $CHCl_3$, molecular sieves 4 Å, 20 °C, 18 h; *v*. DIBAL-H, CH_2Cl_2, −78 °C, 15 min; *vi*. PBr_3, PhMe, 0 °C, 24 h; *vii*. $NaBH_3CN$, HMPA, 70 °C, 1 h.

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furnished β-chloroenal **3** in 80% yield. Compound **3** was cross-coupled with 4-bromophenylboronic acid employing the modified published procedure[6]. Mild oxidation of the resulted aldehyde **4** by sodium chlorite[7] afforded acid **5** in 85% yield. It is of note that the use of the other oxidants including silver oxide and the Jones reagent resulted in recovering of the starting aldehyde, low yield of acid **5** or complex mixture of products of oxidizing of tetrahydrofluorene system. For the intramolecular cyclization of acid **5**, two methods were applied. The first method involved transformation of acid **5** into the corresponding acid chloride and subsequent intramolecular acylation of the latter by treatment with $AlCl_3$ to give tetrahydrofluorenone **6** in 72% yield. The second method is the cyclization of acid **5** using trifluoroacetic anhydride in the presence of molecular sieves 4 Å in chloroform; in this case the yield of **6** was 84%. Reduction of ketone **6** by diisobutylalumohydride (DIBAL-H) under mild conditions afforded alcohol **7** in 96% yield. Subsequent replacement of hydroxy group by bromine atom using phosphorus tribromide furnished dibromide **8** in 72% yield. Chemoselective reduction of the bromine atom at the position 9 of the fluorene system of **8** by sodium cyanoborohydride in HMPA[8] gave the target product **1** in 75% yield.

The suggested synthetic approach can be used for preparing the similar tetrahydrofluorene derivatives.

Experimental

The progress of the reactions was monitored by TLC on Merck Kieselgel 60 F_{254} plates with visualization by the UV light (λ = 254 nm). Melting points of starting and synthesized compounds were determined on a Mettler-FP-90 apparatus equipped with polarizing microscope Olympus BH-2. The purity of starting compounds and products were monitored by gas-liquid chromatography on a Crystall 2000M chromatograph equipped with flame ionizing detector, column length was 1—3 m, (d = 4 mm), stationary phase was 5% XE-60 on Chromaton N-AW-DMCS (0.2—0.25 mm), carrier gas was helium (flow rate is 30 mL min^{-1}), flow rate of hydrogen was 25 mL min^{-1}, flow rate of air was 250 mL min^{-1}, temperature of injector was 200—280 °C, temperature of detector was 300 °C, temperature of the columns was 50—250 °C. ^{1}H NMR spectra were recorded with Bruker AM-300 and Bruker Avance II 300 instruments in $CDCl_3$. Chemical shifts are given in the δ scale relative to Me_4Si. Mass spectra (EI, 70 eV) were recorded on a Kratos MS-30 instrument.

4-Pentylcyclohexanone (2) was synthesized according the known procedure.[9] B.p. 95—98 °C (1.0 Torr) (*cf.* Ref. 9: b.p. 98—100 °C (0.1 Torr)), n_D^{20} 1.4550.

2-Chloro-5-pentylcyclohex-1-ene-1-carboxaldehyde (3). To a solution of DMF (10.3 mL) in chloroform (25 mL), $POCl_3$ (10.1 mL) was added at 5—10 °C and the mixture was stirred for 10 min. Then a solution of 4-pentylcyclohexanone (**2**) (16.8 mL, 0.1 mol) in chloroform (25 mL) was added dropwise at 20 °C. The reaction mixture was heated at 55—60 °C for 3 h and poured into solution of AcONa (35 g) in water (120 ml). The product was extracted with chloroform (3×30 mL), the combined organic layers were washed with water, dried with Na_2SO_4, and the solvent was removed *in vacuo*. Yield 80%, b.p. 92—94 °C (0.240 Torr), n_D^{20} 1.4925. MS, m/z: 214 $[M]^+$. NMR ^{1}H ($CDCl_3$), δ: 10.17 (s, 1 H, CHO); 2.65—2.49 (m, 3 H, CH_2, CH, cycl.); 1.91—1.67 (m, 2 H, CH_2, cycl.); 1.59—1.42 (m, 2 H, CH_2, cycl.); 1.33—1.2 (m, 8 H, CH_2, alkyl); 0.87 (t, 3 H, CH_3, J = 6.6 Hz). Found (%): C, 67.05; H, 8.94. $C_{12}H_{19}ClO$. Calculated (%): C, 67.12; H, 8.92.

2-(4-Bromophenyl)-5-pentylcyclohex-1-ene-1-carboxaldehyde (4). A mixture of compound **3** (0.56 g, 2.59 mmol), 4-bromophenylboronic acid (0.57 g, 2.83 mmol), tetrabutylammonium bromide (0.84 g, 2.60 mmol), 10% Pd/C, K_2CO_3 (0.89 g, 6.45 mmol) and deionized water (5 mL) was stirred at 85 °C for 6 h. The reaction mixture was diluted with water (15 mL) and the products were extracted with AcOEt (3×30 mL), organic layer was separated and stirred with charcoal for 30 min, dried with Na_2SO_4, and the solvent was removed *in vacuo*. The product was distilled under reduced pressure. Yield 68%, b.p. 183—190 °C (0.120 Torr), n_D^{20} 1.5660, m.p. 28—30 °C. MS, m/z: 334 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ: 9.48 (s, 1 H, CHO); 7.52 (d, 2 H, CH, Ar, J = 8.4 Hz); 7.07 (d, 2 H, CH, Ar, J = 8.1 Hz); 2.68—2.49 (m, 3 H, CH_2, CH, cycl.); 1.94—1.50 (m, 4 H, CH_2, cycl.); 1.42—1.21 (m, 8 H, CH_2, alkyl); 0.90 (t, 3 H, CH_3, J = 6.8 Hz). Found (%): C, 64.59; H, 6.94. $C_{18}H_{23}BrO$. Calculated (%): C, 64.48; H, 6.91.

2-(4-Bromophenyl)-5-pentylcyclohex-1-ene-1-carboxylic acid (5). A solution of $NaClO_2$ (1.22 g, 11.2 mmol) in water (10 mL) was added dropwise to a stirred mixture of solutions of aldehyde **4** (2.45 g, 7.32 mmol) in MeCN (30 mL), NaH_2PO_4 (0.350 g, 2.26 mmol) in water (3 mL), and 30% aqueous H_2O_2 (3.8 mL) cooled to 10 °C. The reaction mixture was stirred for 12 h at ambient temperature. Then Na_2SO_3 (0.5 g) was added and the mixture was acidified with 10% aqueous HCl. The precipitate that formed was filtered off and the product was purified by chromatography (SiO_2, elution with EtOAc). Yield 85%, m.p. 119—120 °C (hexane). MS, m/z: 350 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ: 10.87 (s, 1 H, OH); 7.42 (d, 2 H, CH, Ar, J = 8.4 Hz); 7.00 (d, 2 H, CH, Ar, J = 8.1 Hz); 2.60 (dd, 1 H, CH, cycl., J = 17.4 Hz, J = 4.2 Hz); 2.42—2.34 (m, 2 H, CH_2, cycl.); 2.01—1.80 (m, 2 H, CH_2, cycl.); 1.66—1.54 (m, 1 H, CH_2, cycl.); 1.41—1.25 (m, 9 H, 1 H CH_2, cycl., and 8 H CH_2, alkyl); 0.90 (t, 3 H, CH_3, J = 6.8 Hz). Found (%): C, 61.42; H, 6.62. $C_{18}H_{23}BrO_2$. Calculated (%): C, 61.54; H, 6.60.

7-Bromo-2-pentyl-1,2,3,4-tetrahydro-9*H*-fluoren-9-one (6). ***A.*** To a solution of acid **5** (0.351 g, 1.0 mmol) in CH_2Cl_2 (2 mL), a solution of $SOCl_2$ (2 mL) and DMF (2 drops) in CH_2Cl_2 (3 mL) was added dropwise over a period of 30 min at ambient temperature. The reaction mixture was stirred for 30 min at room temperature and refluxed for 15 min, then the solvent was removed *in vacuo*. The resulting acid chloride was dissolved in CH_2Cl_2 (2 mL) and added dropwise to a solution of $AlCl_3$ (0.152 g, 1.14 mmol) in CH_2Cl_2 (2 mL) at ambient temperature. The mixture was stirred for 30 min, poured into cold water (10 mL), extracted with CH_2Cl_2 (3×30 mL), the combined organic layers were washed with water, aqueous $NaHCO_3$, and dried with Na_2SO_4. The solvent was removed *in vacuo*, the residue was purified by chromatography (silica gel, elution with EtOAc—hexane, 1 : 9). Yield 72%, m.p. 77—79 °C (EtOH). MS, m/z: 332 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ: 7.46—7.41 (m, 2 H, CH, Ar); 6.81 (d, 1 H, CH, Ar, J = 7.3 Hz); 2.59—2.32 (m, 3 H, CH_2, CH, cycl.); 2.01—1.92 (m, 1 H, CH_2, cycl.); 1.81—1.55 (m, 2 H,

CH_2, cycl.); 1.43—1.25 (m, 9 H, 1 H CH_2, cycl., and 8 H CH_2, alkyl); 0.90 (t, 3 H, CH_3, J = 6.8 Hz). Found (%): C, 64.71; H, 6.37. $C_{18}H_{21}BrO$. Calculated (%): C, 64.87; H, 6.35.

B. To a solution of acid **5** (100 mg, 0.29 mmol) in anhydrous $CHCl_3$ (2 mL) trifluoroacetic anhydride (0.04 mL, 0.3 mmol) and molecular sieves 4 Å (150 mg) were added. The reaction mixture was stirred at ambient temperature for 18 h, filtered, and the solvent was removed *in vacuo*. The viscous residue was triturated with MeOH (10 mL), the precipitate that formed was recrystallized from EtOH. Yield 84%, m.p. 76—78 °C.

7-Bromo-2-pentyl-1,2,3,4-tetrahydro-9*H*-fluoren-9-ol (7). To a solution of ketone **6** (0.29 g, 0.877 mmol) in CH_2Cl_2 (9 mL), DIBAL-H (1 mL, 1.0 *M* solution in hexane) was added dropwise at −78 °C. After 15 min, MeOH (0.1 mL) was added dropwise at the same temperature, and the reaction mixture was warmed to ambient temperature, then water (2 mL) was added and the mixture was acidified with 1 *M* HCl (20 mL), and the product was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed *in vacuo*. Yield 96%, m.p. 122—124 °C (hexane). MS, *m/z*: 334 $[M^+]$. ^{1}H NMR ($CDCl_3$), δ: 7.57 (s, 1 H, CH, Ar); 7.38 (d, 1 H, CH, Ar, J = 8.8 Hz); 6.93 (d, 1 H, CH, Ar, J = 7.7 Hz); 4.86 (s, 1 H, OH); 2.65—2.21 (m, 3 H, CH_2, CH, cycl.); 2.11—1.63 (m, 4 H, 3 H CH_2, cycl., and 1 H C<u>H</u>OH); 1.43—1.24 (m, 9 H, 1 H, CH_2, cycl., and 8 H CH_2, alkyl); 0.91 (t, 3 H, CH_3, J = 6.5 Hz). Found (%): C, 64.34; H, 6.93. $C_{18}H_{23}BrO$. Calculated (%): C, 64.48; H, 6.91.

7,9-Dibromo-2-pentyl-1,2,3,4-tetrahydro-9*H*-fluorene (8). To a solution of alcohol **7** (0.837 g, 2.5 mmol) in toluene (10 mL), PBr_3 (0.1 mL, 1.2 mmol) was added dropwise at 0 °C. After 24 h, the mixture was cooled to −10 °C, 10% aqueous $NaHCO_3$ (10 mL) was added, and the product was extracted with CH_2Cl_2 (3×15 mL). The combined organics were dried with $MgSO_4$, the solvent was removed *in vacuo*, and the residue was recrystallized from hexane. Yield 72%, m.p. 98—100 °C. MS, *m/z*: 398 $[M^+]$. ^{1}H NMR ($CDCl_3$), δ: 7.59 (s, 1 H, CH, Ar); 7.36 (d, 1 H, CH, Ar, J = 8.7 Hz); 6.90 (d, 1 H, CH, Ar, J = 7.7 Hz); 2.60—2.23 (m, 3 H, CH_2, CH, cycl.); 2.00—1.67 (m, 4 H, 3 H CH_2, cycl., and 1 H CHBr); 1.43—1.26 (m, 9 H, 1 H CH_2, cycl., and 8 H CH_2, alkyl); 0.90 (t, 3 H, CH_3, J = 6.7 Hz). Found (%): C, 54.46; H, 5.58. $C_{18}H_{22}Br_2$. Calculated (%): C, 54.30; H, 5.57.

7-Bromo-2-pentyl-2,3,4,9-tetrahydro-1*H*-fluorene (1). To a solution of dibromide **8** (0.398 g, 1.0 mmol) in HMPA (5 mL), $NaBH_3CN$ (0.256 g, 4 mmol) was added and the mixture was heated at 70 °C for 1 h. Then water (10 mL) was added and the mixture was extracted with diethyl ether (3×15 mL). The combined organics were dried with $MgSO_4$, the solvent was removed *in vacuo*, and the product was purified by chromatography (silica gel, elution with hexane). Yield 75%, m.p. 78—80 °C. MS, *m/z*: 318 $[M]^+$. ^{1}H NMR ($CDCl_3$), δ: 7.49 (s, 1 H, CH, Ar); 7.37 (d, 1 H, CH, Ar, J = 8.1 Hz); 7.03 (d, 1 H, CH, Ar, J = 8.1 Hz); 3.20 (s, 2 H, CH_2, cycl.); 2.57—2.28 (m, 3 H, CH_2, CH, cycl.); 2.09—1.90 (m, 2 H, CH_2, cycl.); 1.79—1.66 (m, 1 H, CH_2, cycl.); 1.45—1.26 (m, 9 H, 1 H CH_2, cycl., and 8 H CH_2, alkyl); 0.93 (t, 3 H, CH_3, J = 6.6 Hz). ^{13}C NMR (DMSO-d_6), δ: 145.06 (C, C=C), 145.01 (C, C=C), 141.91 (C, Ar), 135.49 (C, Ar), 129.04 (C, Ar), 126.61 (C, Ar), 118.73 (C—Br), 117.49 (C, Ar), 40.53 (CH_2), 36.41 (C_{tert}), 34.44, 32.54, 32.23, 29.03, 26.87, 22.80, 22.00 (CH_2), 14.21 (CH_3). Found (%): C, 67.63; H, 7.24. $C_{18}H_{23}Br$. Calculated (%): C, 67.71; H, 7.26.

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