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Synthesis of 4*H*-thieno[3,2-*c*][1]benzopyran-2-carboxaldehydes

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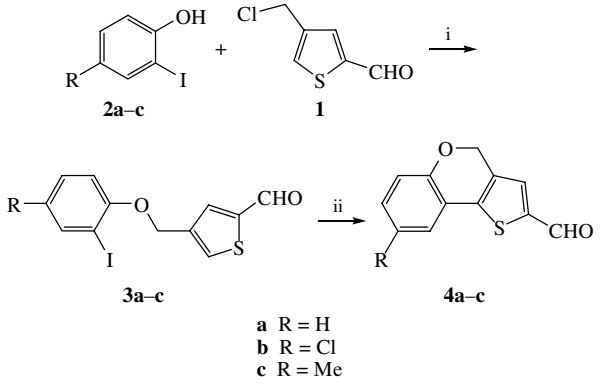
The title compounds were synthesised by the palladium-catalysed intramolecular cyclization of 4-(2-iodoaryloxymethyl)-thiophene-2-carboxaldehydes.

4*H*-Thieno[3,2-*c*][1]benzopyrans are of interest due to their anti-inflammatory and antiparkinsonian activities.[1] However, well-known synthetic methods often imply multi-step and laborious syntheses.[1,2] Surprisingly, intramolecular arylation, which was used for the synthesis of benzopyran derivatives,[3] was not employed for the preparation of 4*H*-thieno[3,2-*c*]-chromenes. Here, we describe a new approach to the above compounds based on such an intramolecular interaction of 4-(2-iodoaryloxymethyl)thiophene-2-carboxaldehydes.

We developed a method for the preparation of 4-aryloxymethyl substituted thiophene-2-carboxaldehydes **3a–c** from 4-chloromethylthiophene-2-carbaldehyde **1**, which can be prepared by the chloromethylation of commercial thiophene-2-carboxaldehyde.[4] Interactions of **1** with corresponding iodophenols **2a–c** give compounds **3a–c**. The reaction was performed in DMF with an excess of potassium carbonate. The yields of 4-substituted thiophene-2-carboxaldehydes **3a–c** were 47–83% (Scheme 1).†



Scheme 1 *Reagents and conditions*: i, K_2CO_3, DMF, room temperature; ii, N_2, K_2CO_3, PPh_3, $Pd(OAc)_2$, hexadecyltrimethylammonium bromide, MeCN, 80 °C, 5 h.

For subsequent chromene ring formation, we used the Heck reaction. Intermolecular thiophene arylation[5] was used for the intramolecular cyclization of 4-(2-iodoaryloxymethyl)thiophene-2-carboxaldehydes **3a–c** (Scheme 1). The cyclization was performed using a Pd catalyst in the presence of triphenylphosphine and an inorganic base (K_2CO_3). Hexadecyltrimethylammonium bromide was used to accelerate this reaction. 4*H*-Thieno[3,2-*c*][1]benzopyran-2-carboxaldehydes **4a–c** were prepared in 20–69% yields.‡ In accordance with published data,[6] the addition of water and the nature of a quaternary ammonium salt influence the yield of the Heck reaction product. However, such an influence was not observed in our case.

† IR spectra were recorded on an Infralum FT-801 instrument in KBr tablets. The ^{1}H and ^{13}C NMR spectra were recorded on a Brucker ARX-300 spectrometer in $CDCl_3$ with TMS as an internal standard. The ^{13}C NMR spectra were measured with complete ^{1}H decoupling.

General procedure for the synthesis of 4-substituted thiophene-2-carboxaldehydes **3a–c**. A mixture of 4-chloromethylthiophene-2-carboxaldehyde **1** (1.6 g, 10 mmol), 2-iodophenol **2a** (2.2 g, 10 mmol), K_2CO_3 (1.4 g, 10 mmol), DMF (5 ml) and a catalytic amount of KI was stirred at room temperature for four days. Then, the reaction mixture was poured into ice-cold water (100 ml) and a crystalline precipitate of **3a** was formed, which was collected by filtration, washed with water, dried and recrystallised from ethanol.

4-(2-Iodophenoxymethyl)thiophene-2-carboxaldehyde **3a**: yield 1.62 g (47%), mp 78 °C (EtOH). ^{1}H NMR, δ: 5.14 (s, 2H, CH_2), 6.74–6.79 (m, 1H, $H_{arom.}$), 6.84–6.87 (m, 1H, $H_{arom.}$), 7.28–7.34 (m, 1H, $H_{arom.}$), 7.79–7.86 (m, 3H, $H_{arom.}$), 9.93 (d, 1H, CHO, ^4J 1.16 Hz). ^{13}C NMR, δ: 66.42 (CH_2), 86.81 (C_{Ar}–I), 131.98 (C_{Th}-5), 135.17 (C_{Th}-3), 182.93 (CHO). Found (%): C, 41.52; H, 2.72. Calc. for $C_{12}H_9IO_2S$ (%): C, 41.88; H, 2.64.

4-(2-Iodo-4-chlorophenoxymethyl)thiophene-2-carboxaldehyde **3b**: yield 2.92 g (77%), mp 105 °C (EtOH). ^{1}H NMR, δ: 5.07 (s, 2H, CH_2), 6.76 (d, 1H, $H_{arom.}$, ^3J 8.79 Hz), 7.26 (dd, 1H, $H_{arom.}$, ^3J 8.79 Hz, ^4J 2.54 Hz), 7.75 (d, 1H, $H_{arom.}$, ^4J 2.54 Hz), 7.81 (s, 1H, 5-H), 7.83 (d, 1H, 3-H, ^4J 1.16 Hz), 9.91 (d, 1H, CHO, ^4J 1.16 Hz). ^{13}C NMR, δ: 66.71 (CH_2), 86.98 (C_{Ar}–I), 132.06 (C_{Th}-5), 135.04 (C_{Th}-3), 182.85 (CHO). Found (%): C, 37.85; H, 2.29. Calc. for $C_{12}H_8ClIO_2S$ (%): C, 38.07; H, 2.13.

4-(2-Iodo-4-methylphenoxymethyl)thiophene-2-carboxaldehyde **3c**. Yield 2.97 g (83%), mp 87 °C (EtOH). ^{1}H NMR, δ: 2.25 (s, 3H, Me), 5.07 (s, 2H, CH_2), 6.73 (d, 1H, $H_{arom.}$, ^3J 8.09 Hz), 7.08 (dd, 1H, $H_{arom.}$, ^3J 8.32 Hz, ^4J 1.62 Hz), 6.61 (d, 1H, $H_{arom.}$, ^4J 1.85 Hz), 7.80 (s, 1H, 5-H), 7.83 (d, 1H, 3-H, ^4J 1.16 Hz), 9.90 (d, 1H, CHO, ^4J 1.16 Hz). ^{13}C NMR, δ: 19.97 (Me), 66.55 (CH_2), 86.68 (C_{Ar}–I), 131.95 (C_{Th}-5), 135.29 (C_{Th}-3), 182.93 (CHO). Found (%): C, 43.22; H, 3.26. Calc. for $C_{13}H_{11}IO_2S$ (%): C, 43.59; H, 3.10.

‡ *General procedure for the synthesis of 4*H*-thieno[3,2-c][1]benzopyran-2-carboxaldehydes* **4a–c**. A suspension of K_2CO_3 (502 mg, 3.6 mmol) and hexadecyltrimethylammonium bromide (531 mg, 1.41 mmol) in MeCN (5 ml) was stirred for 20 min in inert atmosphere. The flask was purged with argon and PPh_3 (38 mg, 0.15 mmol), 4-(2-iodophenoxymethyl)thiophene-2-carboxaldehyde **3a** (500 mg, 1.4 mmol) and $Pd(OAc)_2$ (24 mg, 0.1 mmol) were successively added. The resulting reaction mixture was refluxed for 5 h maintaining inert atmosphere, then poured into water (40 ml), extracted with diethyl ether (3×15 ml). The extracts were washed with brine, dried over Na_2SO_4 and the solvents were removed *in vacuo*. The residue was flash-chromatographed (aluminia/CH_2Cl_2–hexane, 1:1) to give product **4a**, which was additionally purified by recrystallization from ethanol.

*4*H*-Thieno[3,2-c][1]benzopyran-2-carboxaldehyde* **4a**: yield 191 mg (63%), mp 113 °C (EtOH). ^{1}H NMR, δ: 5.27 (s, 2H, CH_2), 6.94–7.41 (m, 4H, $H_{arom.}$), 7.47 (s, 1H, H-3), 9.85 (s, 1H, CHO). ^{13}C NMR, δ: 65.62 (C-4), 117.14 (C-6), 122.4 (C-8), 124.12 (C-9), 131.3 (C-7), 132.89 (C-3), 182.30 (CHO). IR (ν/cm^{-1}): 1660 (C=O), 3058 (C_{Ar}–H). Found (%): C, 66.21; H, 3.85. Calc. for $C_{12}H_8O_2S$ (%): C, 66.65; H, 3.73.

Note that the yields of compounds **3a**–**c** as well as the yields of intermolecular reactions,[5] depend on substituents at the 4-position of the aryl fragment.

Thus, we developed the synthesis of substituted 4*H*-thieno-[3,2-*c*][1]benzopyran-2-carboxaldehydes by the intramolecular cyclization of 4-(2-iodoaryloxymethyl)thiophene-2-carboxaldehydes under Heck reaction conditions.

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*8-Chloro-4*H*-thieno[3,2-*c*][1]benzopyran-2-carboxaldehyde* **4b**: yield 70 mg (20%), mp 192 °C (EtOH). ^{1}H NMR, δ: 5.28 (s, 2H, CH_2), 6.90 (d, 1H, H-6, $J_{H6–H7}$ 8.79 Hz), 7.19 (dd, 1H, H-7, $J_{H6–H7}$ 8.79 Hz, $J_{H7–H9}$ 2.31 Hz), 7.35 (d, 1H, H-9, $J_{H9–H7}$ 2.31 Hz), 7.49 (s, 1H, H-3), 9.87 (s, 1H, CHO). ^{13}C NMR, δ: 65.78 (C-4), 118.53 (C-6), 123.58 (C-9), 130.8 (C-7), 132.62 (C-3), 182.26 (CHO). IR (ν/cm^{-1}): 1648 (C=O), 3073 (C_{Ar}–H). Found (%): C, 57.10; H, 2.97. Calc. for $C_{12}H_7ClO_2S$ (%): C, 57.49; H, 2.81.

*8-Methyl-4*H*-thieno[3,2-*c*][1]benzopyran-2-carboxaldehyde* **4c**: yield 223 mg (69%), mp 136 °C (EtOH). ^{1}H NMR, δ: 2.31 (s, 3H, Me), 5.23 (s, 2H, CH_2), 6.85 (d, 1H, H-6, $J_{H6–H7}$ 8.32 Hz), 7.06 (dd, 1H, H-7, $J_{H6–H7}$ 8.32 Hz, $J_{H7–H9}$ 1.62 Hz), 7.19 (d, 1H, H-9, $J_{H9–H7}$ 1.62 Hz), 7.47 (s, 1H, H-3), 9.84 (s, 1H, CHO). ^{13}C NMR, δ: 20.56 (Me), 65.56 (C-4), 116.89 (C-6), 124.35 (C-9), 131.99 (C-7), 132.98 (C-3), 182.30 (CHO). IR (ν/cm^{-1}): 1666 (C=O), 3062 (C_{Ar}–H). Found (%): C, 67.47; H, 4.51. Calc. for $C_{13}H_{10}O_2S$ (%): C, 67.80; H, 4.38.

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