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Communication

Synthesis and Analytical Characterization of Cyclization Products of 3-Propargyloxy-5-benzyloxy-benzoic Acid Methyl Ester

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Abstract: In the context of our ongoing studies on chromane derivatives as inhibitors of the salicylate synthase from *M. tuberculosis*, we isolated a new, unexpected compound from the cyclization of 3-(propargyloxy)-5-benzyloxy-benzoic acid methyl ester. Its molecular structure was elucidated by means of 1D and 2D NMR analyses, FT-IR, ESI-MS, and HRMS.

Keywords: chromane derivatives; ring-closure; NMR spectroscopy; antitubercular agent

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1. Introduction

Chromane is a bicyclic scaffold, ubiquitous in a wide variety of bioactive natural products and synthetic compounds exhibiting antitumor, anti-inflammatory, antiviral, antiprotozoal, and antimicrobial effects [1–10]. Among them, some have also shown moderate-to-good antitubercular activities [11–18].

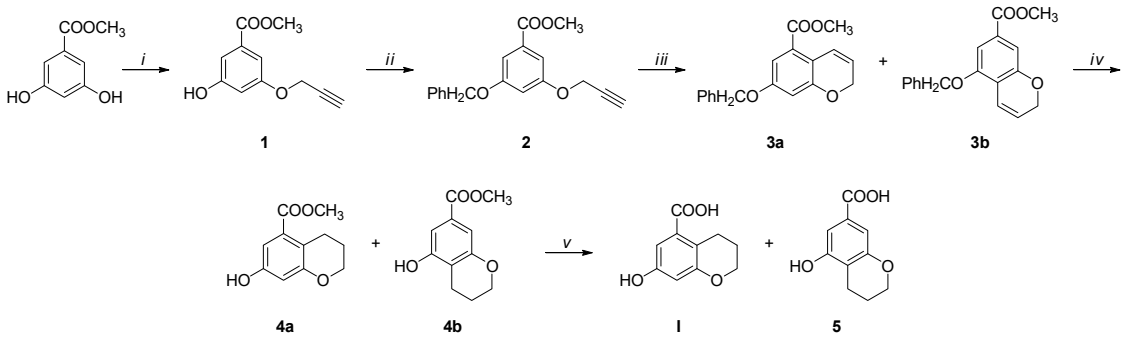
As part of a project focusing on the design and synthesis of new inhibitors of the salicylate synthase MbtI from *M. tuberculosis* [19–26], we investigated several heterocyclic cores [27–30], including the chroman-4-one and chromane scaffolds [31,32]. Our studies led to the synthesis of a pool of derivatives, which were tested for their inhibitory effect towards this target, demonstrating promising activities [31,32].

With the aim of synthesizing 7-hydroxychroman-5-carboxylic acid **I** (Figure 1), we attempted the reduction of the corresponding 4-chromanone, following the approach used in our previous work [31]. However, this hydrogenation reaction, catalyzed by palladium on barium sulphate, was unsuccessful. The same outcome was obtained using different catalysts, including palladium on carbon (10%), or other reducing agents, such as zinc/acetic acid, hydrazine, and *tert*-butylamine–borane complex. Therefore, we developed a different strategy, which is discussed in the following paragraphs. This new approach led to the obtainment of an unexpected byproduct, which was isolated, characterized, and then used in the following steps to yield a new product (**5**).

Figure 1. The desired 7-hydroxychroman-5-carboxylic acid (**I**) and the unexpected 5-hydroxychroman-7-carboxylic acid (**5**), obtained from a byproduct of the new synthetic approach.

2. Results and Discussion

Considering our difficulties in obtaining the desired compound **I** by the same method developed for the previous derivatives [31], we implemented a new synthetic pathway, shown in Scheme 1.



Scheme 1. Reagents and conditions: (*i*) $CH{\equiv}CCH_2Br$, K_2CO_3, 18-Crown-6, N_2, DMF, 48 h, reflux; (*ii*) CH_3OH, PPh_3, DIAD, N_2, 0 °C → RT, 24 h or $PhCH_2Br$, K_2CO_3, N_2, 4 h, reflux; (*iii*) DEA, N_2, 24 h, 210 °C; (*iv*) 10% H_2/Pd-C, MeOH, RT, 6 h; (*v*) NaOH, H_2O/MeOH, 3 h, 58 °C.

The mono-alkyl methyl benzoate **1** was obtained from the OH alkylation of 3,5-dihydroxymethylbenzoate using propargyl bromide, 18-crown-6, and anhydrous potassium carbonate in anhydrous dimethylformamide at 80 °C for 48 h. Compound **1** was purified from the 3,5 dialkyl derivative by column chromatography. Subsequently, the hydroxyl group was protected upon treatment with benzyl bromide, before being cyclized in *N*,*N*-diethyl aniline at 210 °C for 24 h, giving a mixture of compounds **3a** and **3b**. The hydrogenation of the mixture of the *O*-benzyl derivatives using 10% palladium on carbon afforded the simultaneous reduction of the double bond and the *O*-deprotection, giving a mixture of compounds **4a** and **4b**, which were easily separated by column chromatography. The obtained methyl esters were separately hydrolyzed to the corresponding carboxylic acids under basic conditions, using sodium hydroxide in a water–methanol mixture. The structure of compounds **4a** and **4b** was studied by mono- and bidimensional NMR techniques, ESI-MS, and FT-IR. NOESY experiments were carried out to unequivocally determine the hydroxyl chromane structures (see Supplementary Materials). The spectrum of compound **4a** revealed a distinct correlation between the OH singlet and the two doublets of the aromatic hydrogens, whereas the spectrum of compound **4b** displayed a weak correlation between the OH and only one of aromatic hydrogens (Figure 2). Finally, high-resolution mass spectrometry (HRMS) was employed to support the NMR and FT-IR analyses, unequivocally confirming the obtainment of the byproduct **5**, hydrolyzed in basic conditions from **4b**.

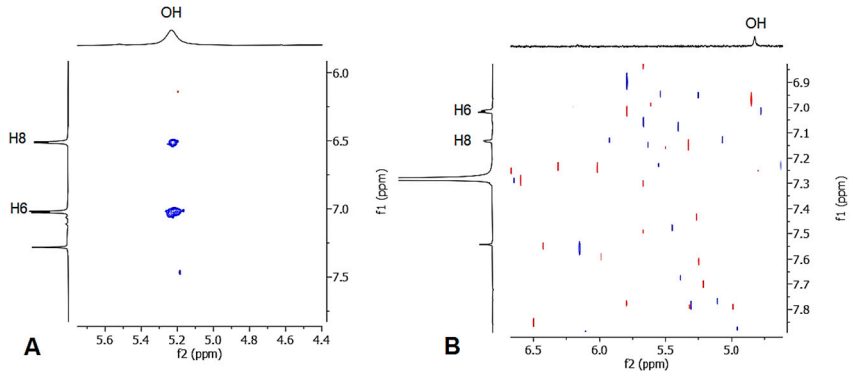


Figure 2. NOESY spectra of compounds **4a** (**A**) and **4b** (**B**).

3. Materials and Methods

All reagents and solvents were purchased from Sigma-Aldrich/Merck (Merck KGaA, Darmstadt, Germany). Reactions involving air-sensitive reagents were carried out using anhydrous solvents, in oven-dried glassware, and under nitrogen atmosphere. The reactions were monitored by TLC analysis on Silica Gel Matrix plates (0.25 nm; Merck), which were visualized under a UV lamp operating at a wavelength of 254 or 365 nm. When

necessary, the spots were evidenced using an ethanolic $KMnO_4$ solution. Melting points were recorded on a Büchi apparatus (Büchi, Flawil, Switzerland) and are uncorrected.

Mono- and bidimensional NMR spectra were recorded at room temperature on a Varian-Mercury Oxford 300 cryomagnet (Oxford Instruments, Abingdon, UK), operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C, or on a Bruker Avance 500 (Billerica, MA, USA) instrument, operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Depending on the solubility of the compound, $CDCl_3$ or DMSO-d_6 were used as deuterated solvents for all spectra run. Chemicals shifts are expressed in ppm (δ) from tetramethylsilane resonance in the indicated solvents; coupling constants (*J*-values) are given in Hertz (Hz). ^{1}H signals are reported in the following order: ppm, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, and assignments. The APT sequence was used to distinguish methyl and methine signals from those due to methylene and quaternary carbons.

FT-IR spectra were recorded on a SPECTRUM ONE (PerkinElmer, Waltham, MA, USA) instrument, using the DATA MANAGER v.2 software (Perkin Elmer), between 4000 and 600 cm^{-1} (liquid samples) or 450 cm^{-1} (solid samples) performing 8 scans at a resolution of 4 cm^{-1}. Liquid samples were deposited on NaCl plates, while solids were mixed in a 1:100 *w/w* ratio with KBr and pressed through a hydraulic press (14 tons) to small tablets.

Mass spectrometry analyses were carried out on a LCQ Advantage (ThermoFisher Scientific, Waltham, MA, USA), equipped with an ESI electrospray ionization source and an Ion Trap mass analyzer; ionization: ESI positive or ESI negative; capillary temperature: 250 °C; source voltage: 5.50 kV; source current: 4.00 μA; multipole 1 and 2 offset, −5.50 V and −7.50 V, respectively; intermultipole lens voltage: −16.00 V; trap DC offset voltage: −10.00 V. The high-resolution mass spectrometry (HRMS) analysis was carried out on a Q-ToF Synapt G2-Si HDMS system (Waters, Milford, MA, USA).

*Synthesis of 3-propargyloxy-5-hydroxy benzoic acid methyl ester (***1***)*

Under a nitrogen flow, 3,5-dihydroxybenzoate (3 g, 17.86 mmol), propargyl bromide (1.70 g, 14.29 mmol), and 18-crown-6 (0.38 g, 1.43 mmol) were dissolved in dry DMF (94 mL). Anhydrous K_2CO_3 (5.43 g, 39.29 mmol) was added, and the reaction was refluxed at 80 °C for 48 h. The mixture was then cooled to room temperature, filtered, and the filtrate was evaporated under vacuum. The crude product was purified by column chromatography using a 4:1 mixture of petroleum ether/EtOAc as the eluent. Yield: 30%. TLC (petroleum ether/EtOAc 8:2): Rf = 0.28. Ivory-colored solid. m.p.: 123–127 °C. FT-IR (KBr): ν 3425, 3294, 3282, 2986, 2929, 2876, 2850, 1714, 1605, 1626, 1600, 1496, 1453, 1434, 1376, 1154 cm^{-1}. ^{1}H NMR (300 MHz, DMSO): δ 9.91 (s exch D_2O, 1H, OH), 6.99 (dd, *J* = 2.1, 1.3 Hz, 1H, H_2), 6.97 (d, *J* = 2.2, *J* = 1.3 Hz, 1H, H_6), 6.62 (t, *J* = 2.2 Hz, 1H, H_4), 4.77 (d, *J* = 2.4 Hz, 2 H, CH_2), 3.80 (s, 3H, CH_3), 3.57 (t, *J* = 2.4 Hz, 1H, CH) ppm. ^{13}C NMR (75 MHz, DMSO): δ 166.4, 159.0, 158.8, 131.9, 109.8, 107.5, 106.6, 79.5, 78.9, 56.1, 52.6 ppm. MS (ESI): *m/z* calcd for $C_{11}H_{10}O_4$ 206.06, found 205.07 $[M - H]^-$.

*Synthesis of 3-propargyloxy-5-benzyloxy-benzoic acid methyl ester (***2***)*

To a solution of compound **1** (300 mg, 1.46 mmol) in anhydrous acetone (6 mL), K_2CO_3 (500 mg, 3.64 mmol) was added under a nitrogen flow. Benzyl bromide (0.27 mg, 1.6 mmol) was dripped, and the reaction mixture heated at 55 °C for 4 h. After cooling to room temperature, the mixture was filtered and evaporated in vacuum, and the crude residue was purified by column chromatography using hexane/EtOAc 8:2. Yield: 42%. TLC (hexane/EtOAc 8:2): Rf = 0.31. Brown solid. m.p.: 123–127 °C. FT-IR (KBr): ν 3294, 3278, 3066, 3009, 2949, 2922, 2871, 2843, 1716, 1605, 1475, 1453, 1442, 1384, 1324, 1236, 1161, 1057 cm^{-1}. ^{1}H NMR (300 MHz, DMSO): δ 7.45–7.24 (m, 7H, $H_{arom,}$ H_2, H_6), 6.80 (t, *J* = 2.4 Hz, 1H, H_4), 5.08 (s, 2 H, CH_2Ph), 4.70 (d, *J* = 2.4 Hz, 2H, H_2), 3.57 (t, *J* = 2.4 Hz, 1H, CH) ppm. ^{13}C NMR (75 MHz, DMSO): δ 166.6, 159.8, 158.6, 136.4, 132.1, 128.6, 128.1, 127.5, 109.0, 108.4, 107.4, 75.8, 70.4, 56.1, 52.3 ppm. MS (ESI): *m/z* calcd for $C_{18}H_{16}O_4$ 296.32, found 295.56 $[M - H]^-$.

*Synthesis of methyl 7-(benzyloxy)-2H-chromene-5-carboxylate (***3a***) and methyl 5-(benzyloxy)-2H-chromene-7-carboxylate (***3b***)*

Under a nitrogen flow, a solution of compound **2** (180 mg, 0.618 mmol) in *N*,*N*-diethylaniline (2.5 mL, 16.83 mmol) was heated at 210 °C for 24 h. After cooling, the mixture was diluted with diethyl ether (5 mL) and washed (4 × 10 mL) with aq. HCl (5%) and brine. The organic phase was dried over Na_2SO_4 and filtered. The crude residue obtained by evaporation in vacuo was purified by column chromatography using hexane/EtOAc 9:1, affording a mixture of compounds **3a** and **3b**. Light-yellow oil. Yield: 56%. TLC (hexane/EtOAc 8:2): Rf= 0.35. FT-IR (KBr): ν 3090, 3066, 3033, 2952, 2918, 2849, 1721, 1609, 1585, 1497, 1454, 1435, 1375, 1302, 1238, 1150, 1029 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.45–7.32 (m, 11H, H_{arom}, H_4-**3b**), 7.22 (m, 2H, H_6-**3b**), 7.13 (d, *J* = 1.3 Hz, 1H, H_6-**3a**), 6.84 (d, *J* = 6.7 Hz, 1H, H_4-**3a**), 6.62 (d, *J* = 1.3 Hz, 1H, H_8-**3a**), 5.86–5.76 (m, 2H, H_3-3a, H_3-**3b**), 5.11 (s, 2H, $\underline{CH_2}$Ph-**3b**), 5.05 (s, 2H, $\underline{CH_2}$Ph-**3a**), 4.82 (m, 2H, H_2-**3b**), 4.82 (m, 2H, H_2-**3a**), 3.88 (s, 6H, CH_3) ppm. MS (ESI): *m*/*z* calcd for $C_{18}H_{16}O_4$ 296.10, found 327.80 $[M + CH_3OH - H]^-$.

*Synthesis of methyl 7-hydroxychromane-5-carboxylate (***4a***) and methyl 5-hydroxychromane-7-carboxylate (***4b***)*

A solution of the mixture of **3a** and **3b** (100 mg, 0.339 mmol) in dry methanol (2.8 mL) was reduced with hydrogen under atmospheric pressure and room temperature over 10% Pd/C (18 mg, 0.0017) for 6 h. The catalyst was filtered off on a celite pad, and the solvent was evaporated under vacuum. The crude residue was purified by column chromatography using cyclohexane/isopropanol 9:1, affording **4a** as a pale-yellow oil, yield 30%, and **4b** as a pale-yellow oil, yield 40%. TLC (cyclohexane/isopropanol 9:1): Rf for **4a** = 0.30 and Rf for **4b** = 0.24. FT-IR for **4a** (KBr): ν 3395, 2952, 2877, 2843, 1716, 1699, 1615, 1589, 1470, 1453, 1436, 1385, 1313, 1271, 1229, 1142, 1073 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) for **4a**: δ 7.00 (d, *J* = 2.7 Hz, 1H, H_6), 6.49 (d, *J* = 2.7 Hz, 1H, H_8), 5.09 (broad s exch D_2O, 1H, OH), 4.20–4.15 (m, 2H, H_2), 3.87 (s, 3H, CH_3), 2.71 (t, *J* = 6.6 Hz, 2H, H_4), 2.05–1.84 (m, 2H, H_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) **4a**: δ 167.5, 156.4, 154.0, 131.1, 116.8, 110.3, 107.8, 66.2, 51.9, 23.4, 22.3 ppm. FT-IR for **4b** (KBr): ν 3433, 3353, 2947, 2870, 2845, 1693, 1615, 1586, 1467, 1435, 1423, 1383, 1308, 1269, 1228, 1142, 1073 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) for **4b**: δ 7.09 (d, *J* = 1.8 Hz, 1H, H_8), 7.08 (d, *J* = 1.8 Hz, 1H, H_6), 5.45 (broad s exch D_2O, 1H, OH), 4.28–3.99 (m, 2H, H_2), 3.87 (s, 3H, CH_3), 3.00 (t, *J* = 6.6 Hz, 2H, H_4), 2.05–1.97 (m, 2H, H_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) for **4b**: δ 166.8, 156,4, 154.1, 128.5, 115.3, 110.8, 107.3, 66.2, 52.1, 21.4, 19.4 ppm.

*Synthesis of 7-hydroxychromane-5-carboxylic acid (***I***)*

A solution of powdered NaOH (6 mg, 0.142 mmol) in a mixture of water (1 mL) and methanol (0.4 mL) was added to compound **4a** (10 mg, 0.048 mmol) and stirred at 55 °C for 3 h. After the evaporation of methanol under reduced pressure, the pH of the solution was adjusted to pH 3–4, by the addiction of 1 M HCl, and the precipitate was recovered by filtration. Yield: 65%. Light-brown solid. TLC (hexane/EtOAc 1:1): Rf = 0.13. FT-IR (KBr): ν 3362, 3070, 2918, 2849, 1688, 1615, 1585, 1489, 1457, 1427, 1384, 1354, 1306, 1275, 1241, 1138 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 12.70 (broad s exch D_2O, 1H, COOH), 9.42 (broad s exch D_2O, 1H, OH), 6.79 (d, *J* = 2.6 Hz, 1H, H6), 6.30 (d, *J* = 2.6 Hz, 1H, H_8), 4.04 (t, *J* = 4.08 Hz, 2H, H_2), 2.83 (t, *J* = 6.5 Hz, 2H, H_4), 1.86–1.78 (m, 2H, H_3) ppm. ^{13}C NMR (125.75 MHz, DMSO): δ 168.8, 156.3, 156.0, 114.5, 110. 3, 108.8, 107.1, 66.0, 23.3, 22.4 ppm. MS (ESI): *m*/*z* calcd for $C_{10}H_{10}O_4$ 194.06, found 193.19 $[M - H]^-$.

*Synthesis of 5-hydroxychromane-7-carboxylic acid (***5***)*

A solution of powdered NaOH (12 mg, 0.284 mmol) in a mixture of water (1 mL) and methanol (0.4 mL) was added to compound **4b** (20 mg, 0.096 mmol) and stirred at 55 °C for 3 h. After the evaporation of methanol under reduced pressure, the pH of the solution was adjusted to pH 3–4 by the addition of 1 M HCl, and the precipitate was recovered by filtration. Yield: 77%. Light-brown solid. TLC (hexane/EtOAc 1:1): Rf = 0.14. FT-IR (KBr): ν 3396, 3206, 3077, 2949, 2927, 2871, 2855, 1682, 1614, 1584, 1512, 1424, 1387, 1348, 1307, 1269,

1144, 1072, 988 cm^{-1}. ^1H NMR (300 MHz, DMSO): δ 12.62 (broad s exch D_2O, 1H, COOH), 9.72 (broad s exch D_2O, 1H, OH), 6.89 (s, 1H, H_6), 6.72 (s, 1H, H_8), 4.04 (t, J = 4.09 Hz, 2H, H_2), 2.54 (t, J = 6.4 Hz, 2H, H_4), 1.90–1.82 (m, 2H, H_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.7, 156.2, 155.8, 129.7, 115.5, 108.8, 107.3, 66.0, 21.5, 19.7 ppm. HRMS (ESI/Q-ToF): *m/z* calcd for $[C_{10}H_{10}O_4 - H]^-$ 193.0501, found 193.0502.

4. Conclusions

Methyl 5-(benzyloxy)-2*H*-chromene-7-carboxylate was obtained as a side product from the cyclization of 3-(propargyloxy)-5-benzyloxy-benzoic acid methyl ester. After simultaneous deprotection of the hydroxyl group and double-bond reduction, the purified compounds were characterized by spectroscopic methods (FT-IR, ^1H and ^{13}C NMR, NOESY, and HSQC). HRMS analysis of the corresponding carboxylic acid was also performed to definitively confirm its identity.

Supplementary Materials: The following are available online, ^1H NMR, ^{13}C NMR, FT-IR, ESI-MS spectra of all compounds, H-H NOESY NMR spectra of compounds **4a** and **4b**, and HRMS of compound **5**.

Author Contributions: Conceptualization of the work: E.P.; synthesis: M.M. and G.C.; analysis and analytical study: E.P. and D.N.; writing—original draft preparation, review, and editing: M.M. and E.P. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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Conflicts of Interest: The authors declare no conflicts of interest.

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