Letters to the Editor

3-Nitrothiochromone: simple synthesis and selected reactions

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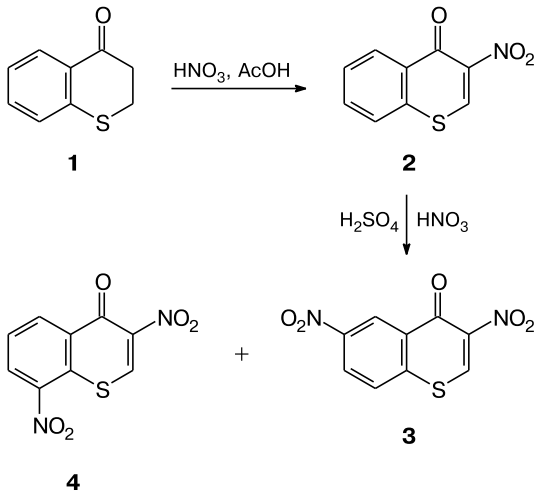
Unlike well-studied 3-nitrochromone,[1—4] 3-nitrothiochromone is much less popular. This compound was mentioned[5] for the first (and hitherto sole) time as the starting reagent for the synthesis of 3-aminothiochromone, the first representative of tyrosine-protein kinase inhibitors with v-*abl*-kinase selectivity. However, the four-step synthesis of 3-nitrothiochromone from not easily accessible 2-mercaptoacetophenone is given schematically,[5] without any experimental (including spectroscopic) data.

When developing new methods for the preparation of 3-substituted thiochromones[6] from commercial thiochroman-4-one (**1**), we found that nitration of the latter with 65% HNO_3 in acetic acid at ~20 °C gives 3-nitrothiochromone (**2**) in 57% yield (Scheme 1). The ^{1}H NMR spectrum of the product obtained shows a singlet for the H(2) proton at δ 8.88 (for unsubstituted thiochromone, the signal for this atom appears at δ 7.82 as a doublet with J = 10 Hz).[7] Thus, we discovered a straightforward and efficient route to 3-nitrothiochromone (**2**), which makes this compound suitable for further investigations.

Treatment of 3-nitrothiochromone (**2**) with a nitrating mixture gives 3,6- and 3,8-dinitrothiochromones **3** and **4** in a total yield of 82%. Their ratio (9 : 1) is evident from the multiplicity of the signals for the aromatic protons. For instance, the ^{1}H NMR spectrum of isomer **3** shows two doublets and a doublet of doublets (^3J = 8.9 Hz, ^4J = 2.6 Hz), which is possible only in the case of 3,6-dinitrothiochromone. The spectrum of isomer **4** shows a triplet with ^3J = 8.1 Hz for the H(6) proton of the 3,8-dinitro

Scheme 1



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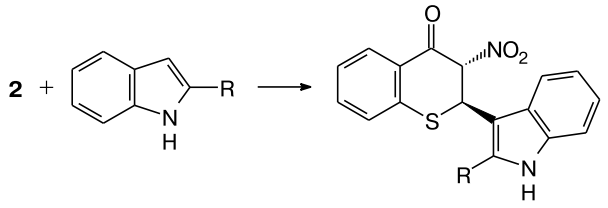
derivative. Its structure agrees with the directing effect of the substituents.

Taking into account that the indole ring is an important structural unit of many natural and biologically active compounds,[8] we studied reactions of 3-nitrothiochromone with indole and 2-methylindole under the conditions described in Ref. 9. As expected, the reaction follows nucleophilic 1,4-addition to the C(2) atom, although without opening the thiopyrone ring, which differs from the reaction pattern for 3-substituted chromones[10—12] (Scheme 2).

Scheme 2



5a,b

R = H (**a**), Me (**b**)

Adducts **5a,b** were obtained in 74—89% yields as one diastereomer with a *trans*-diequatorial arrangement of the substituents ($^3J_{H(2),H(3)}$ = 13.3 Hz). As with 3-chlorothiochroman-4-one described earlier,[7] the NMR spectra of compounds **5** contain signals at δ 8.10 (H(5)) and 186.0 (C=O), which provide evidence for the thiochromanone structure. Adduct **5a** was isolated as a 1 : 0.5 conglomerate with the starting indole.

3-Nitrothiochromone (2). Nitric acid (38.0 g, 0.39 mol) as a 65% solution was added dropwise to a stirred solution of thiochroman-4-one (**1**) (12.5 g, 0.076 mol) in acetic acid (200 mL). The reaction mixture was stirred at ~20 °C for 14 h and then poured into water (800 mL). The yellow precipitate that formed was filtered off, washed with water, and dried in air. The yield was 9.0 g (57%), m.p. 155—156 °C. Found (%): C, 52.10; H, 2.46; N, 6.51. $C_9H_5NO_3S$. Calculated (%): C, 52.17; H, 2.43; N, 6.76. IR (KBr, ν/cm^{-1}): 3014, 1655, 1636, 1591, 1545, 1509. ^{1}H NMR (200 MHz, $CDCl_3$), δ: 7.63—7.75 (m, 3 H, H(6), H(7), H(8)); 8.63—8.68 (m, 1 H, H(5)); 8.88 (s, 1 H, H(2)). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 7.73 (t, 1 H, H(7), *J* = 7.7 Hz); 7.85 (t, 1 H, H(6), *J* = 7.2 Hz); 8.06 (d, 1 H, H(8), *J* = 8.0 Hz); 8.41 (d, 1 H, H(5), *J* = 7.7 Hz); 9.58 (s, 1 H, H(2)). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 128.4, 128.9, 129.7, 133.2, 133.5, 135.8, 143.3, 143.5, 170.2.

3,6-Dinitrothiochromone (3). A solution of 3-nitrothiochromone (**2**) (150 mg, 0.72 mmol) in a mixture of conc. H_2SO_4 (1 mL, 1.84 g, 17.8 mmol) and 97% HNO_3 (0.2 mL, 300 mg, 4.62 mmol) was stirred at 130 °C for 30 min. Then the reaction mixture was cooled and poured onto crushed ice (20 g). The precipitate that formed was filtered off, washed with water to a neutral reaction, and dried. The yield was 0.15 g (82%), a cream-colored powder, m.p. 185—190 °C. Found (%): C, 42.95; H, 1.76; N, 11.04. $C_9H_4N_2O_5S$. Calculated (%): C, 42.86; H, 1.60; N, 11.11. Compound **3** (90%). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 8.42 (d, 1 H, H(8), *J* = 8.9 Hz); 8.61 (dd, 1 H, H(7), *J* = 8.9 Hz, *J* = 2.6 Hz); 9.05 (d, 1 H, H(5), *J* = 2.6 Hz); 9.69 (s, 1 H, H(2)). 3,8-Dinitrothiochromone **4** (10%). ^{1}H NMR (400 MHz, DMSO-d_6), δ: 8.00 (t, 1 H, H(6), *J* = 8.1 Hz); 8.88 (dd, 1 H, H(5/7), *J* = 8.1 Hz, *J* = 1.5 Hz); 8.90 (dd, 1 H, H(7/5), *J* = 8.1 Hz, *J* = 1.5 Hz); 9.67 (s, 1 H, H(2)).

2-(Indol-3-yl)-3-nitrothiochroman-4-one (5a), as a 1 : 0.5 conglomerate with indole. A mixture of 3-nitrothiochromone (**2**) (150 mg, 0.72 mmol) and indole (260 mg, 2.2 mmol) was heated at 80 °C for 1 h. The precipitate was diluted with hexane, filtered off, washed with boiling hexane (10×3 mL), and dried. The yield was 205 mg (74%), a brown powder, m.p. 195—196 °C. Found (%): C, 66.16; H, 4.33; N, 9.44. $C_{17}H_{12}N_2O_3S \cdot 0.5C_8H_7N$. Calculated (%): C, 65.87; H, 4.08; N, 9.14. IR (KBr, ν/cm^{-1}): 3412, 3365, 1693, 1583, 1550. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 5.96 (d, 1 H, H(3), *J* = 13.3 Hz); 7.06 (ddd, 1 H, H(5′/6′), *J* = 8.0 Hz, *J* = 7.0 Hz, *J* = 1.0 Hz); 7.15 (ddd, 1 H, H(6′/5′), *J* = 8.0 Hz, *J* = 7.0 Hz, *J* = 1.0 Hz); 7.17 (d, 1 H, H(2), *J* = 13.3 Hz); 7.36—7.46 (m, 3 H, H(6), H(4′), H(7′)); 7.59 (d, 1 H, H(2′), *J* = 2.6 Hz); 7.64 (ddd, 1 H, H(7), *J* = 8.0 Hz, *J* = 7.3 Hz, *J* = 1.5 Hz); 7.89 (d, 1 H, H(8), *J* = 8.0 Hz); 8.10 (dd, 1 H, H(5), *J* = 8.0 Hz, *J* = 1.5 Hz); 11.36 (br.s, 1 H, NH). Indole. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 6.41 (ddd, 1 H, H(3), *J* = 3.0 Hz, *J* = 2.0 Hz, *J* = 0.9 Hz); 6.97 (ddd, 1 H, H(5/6), *J* = 8.0 Hz, *J* = 7.0 Hz, *J* = 1.1 Hz); 7.06 (ddd, 1 H, H(6/5), *J* = 8.0 Hz, *J* = 7.0 Hz, *J* = 1.1 Hz); 7.32 (t, 1 H, H(2), *J* = 2.8 Hz); 7.37 (d, 1 H, H(4/7), *J* = 7.9 Hz); 7.53 (d, 1 H, H(7/4), *J* = 7.9 Hz); 11.06 (br.s, 1 H, NH).

2-(2-Methylindol-3-yl)-3-nitrothiochroman-4-one (5b) was obtained analogously. The yield was 89%, a beige powder, m.p. 179—180 °C. Found (%): C, 63.75; H, 4.23; N, 8.15. $C_{18}H_{14}N_2O_3S$. Calculated (%): C, 63.89; H, 4.17; N, 8.28. IR (KBr, ν/cm^{-1}): 3422, 1669, 1583, 1554. ^{1}H NMR (400 MHz, DMSO-d_6), δ: 2.41 (s, 3 H, Me); 5.88 (d, 1 H, H(3), *J* = 13.4 Hz); 7.00 (ddd, 1 H, H(5′/6′), *J* = 8.0 Hz, *J* = 7.0 Hz, *J* = 1.1 Hz); 7.06 (ddd, 1 H, H(6′/5′), *J* = 8.0 Hz, *J* = 7.0 Hz, *J* = 1.1 Hz); 7.23 (d, 1 H, H(2), *J* = 13.4 Hz); 7.29 (d, 1 H, H(4′/7′), *J* = 7.9 Hz); 7.37 (ddd, 1 H, H(6), *J* = 8.0 Hz, *J* = 7.2 Hz, *J* = 1.1 Hz); 7.46 (d, 1 H, H(7′/4′), *J* = 7.9 Hz); 7.63 (ddd, 1 H, H(7), *J* = 8.0 Hz, *J* = 7.2 Hz, *J* = 1.5 Hz); 7.91 (d, 1 H, H(8), *J* = 8.0 Hz); 8.10 (dd, 1 H, H(5), *J* = 8.0 Hz, *J* = 1.5 Hz); 11.26 (s, 1 H, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ: 11.8, 94.1, 102.5, 111.5, 119.5, 119.7, 121.3, 126.0, 127.4, 129.4, 130.1, 135.2, 135.7, 136.6, 142.6, 186.0.

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