Self-condensation of 3-cyanothiochromone upon the action of benzyl- and phenethylamine

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Reflux of 3-cyanothiochromone with benzylamine in toluene afforded 17-benzyl-6,7,14,15-tetrahydro-7,15-epiminobis(8*H*,16*H*-dithiochromeno)[2,3-*b*:2´,3´-*f*][1,5]diazocine-6,14-dione, the self-condensation product of 2-amino-3-(benzyliminomethyl)thiochromone. Similar reaction with phenethylamine leads to 2-(thiochromon-3-yl)-5*H*-thiochromeno[2,3-*d*]pyrimidin-5-one. Mechanism of formation of the dimeric products was considered.

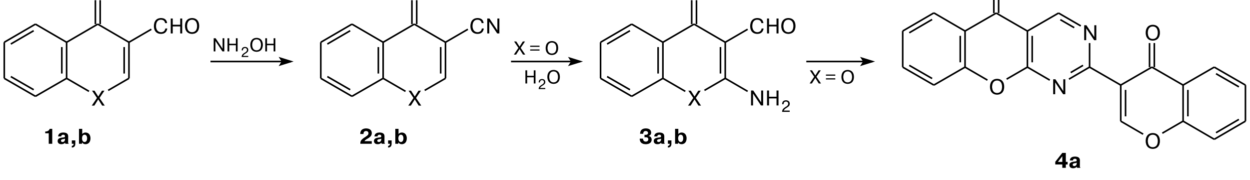
Key words: 3-cyanothiochromone, benzylamine, phenethylamines, self-condensation, 17-benzyl-6,7,14,15-tetrahydro-7,15-epiminobis(8*H*,16*H*-dithiochromeno)[2,3-*b*:2´,3´-*f*]-[1,5]diazocine-6,14-dione, 2-(4-oxo-4*H*-thiochromen-3-yl)-5*H*-thiochromeno[2,3-*d*]pyrimidin-5-one.

It is known that treatment of 3-formylchromone (**1a**) and 3-formylthiochromone (**1b**) with hydroxylamine easily leads to the formation of 3-cyanochromone (**2a**)[1,2] and 3-cyanothiochromone (**2b**).[3] Chemical properties of 3-cyanochromone (**2a**) were studied in detail.[4] One of its most important reactions is the reaction with water, which yields 2-amino-3-formylchromone (**3a**)[5,6] capable of self-condensation to 2-(4-oxo-4*H*-chromen-3-yl)-5*H*-chromeno[2,3-*d*]pyrimidin-5-one (**4a**)[7,8] (Scheme 1). Unlike for **2a**, data on the reactivity of 3-cyanothiochromone (**2b**) are absent in the literature.

Results and Discussion

While studying[9] chemical properties of thiochromones **1b** and **2b**, we failed in the transformation **2b** → **3b** under conditions used earlier[5,6] for the preparation of amino aldehyde **3a**, that is apparently due to higher aromaticity of the thiopyrone ring and lower electrophilicity of the C(2) atom, which hinders addition of the water molecule at this atom and cleavage of the S—C(2) bond. Nevertheless, reflux of nitrile **2b** with benzylamine in the presence of Et_3N in toluene for 1 h led to 72% isolated yield of imine of the target chromone **3b**, *viz.*, 2-amino-3-(benzyliminomethyl)thiochromone (**5**). Further treatment of **5** with benzylamine (toluene, Et_3N, reflux, 12 h) revealed a new direction of the reaction, which is uncharacteristic of the chromone system. It turned out that under these conditions, imine **5** dimerizes to 2,6,9-triazabicyclo-[3.3.1]nonane **6** in 28% yield, which increases to 37% if the reaction is carried out directly from **2b** without isolation of the intermediate imine **5**. As far as we know,

Scheme 1



X = O (**a**), S (**b**)

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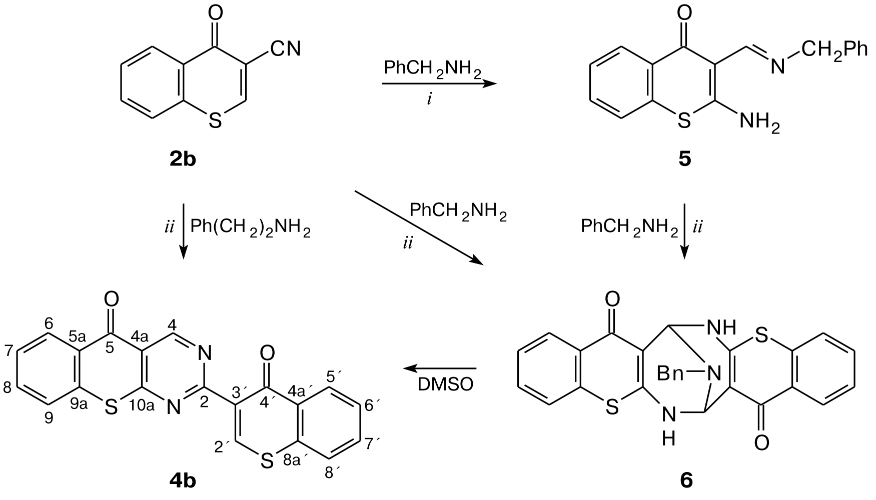
Scheme 2

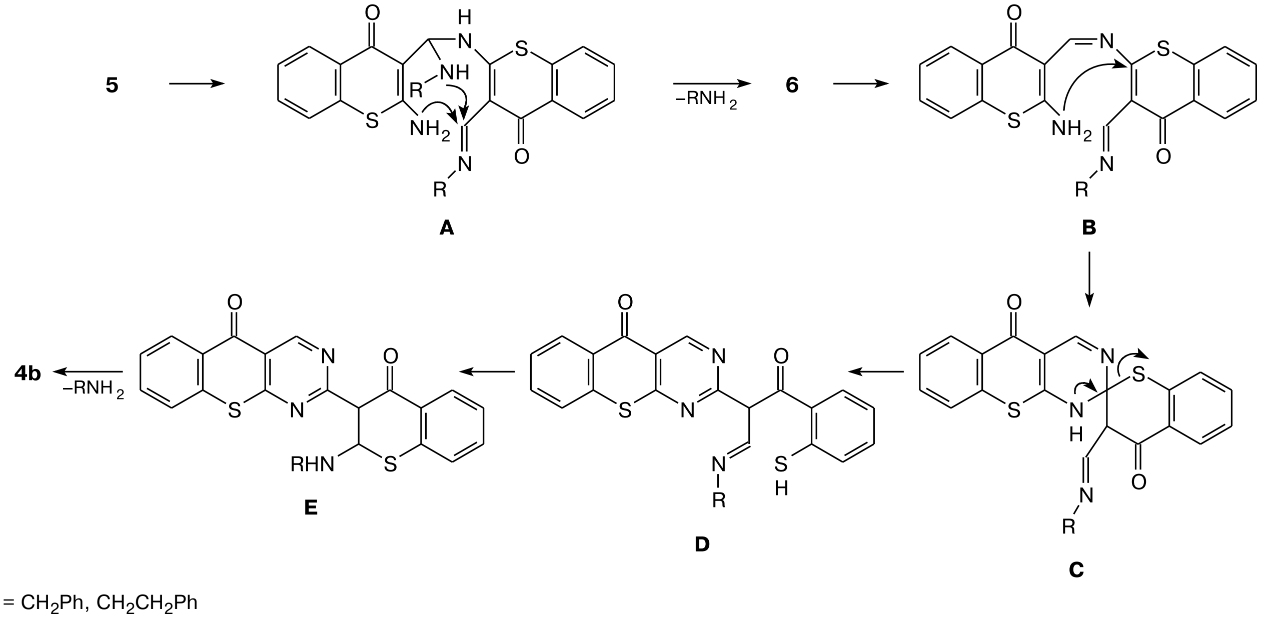


Reaction conditions: *i*. $PhCH_3$, Et_3N, reflux 1 h; *ii*. $PhCH_3$, Et_3N, reflux 10—12 h.

derivatives obtained earlier[10] by the reaction of 5-amino-3,4-diphenylthieno[2,3-*c*]pyridazine-6-carbaldehyde with aliphatic primary amines were the only example of 1,5-diazocines fused with a heterocyclic system. Note that similar reaction of 3-cyanothiochromone (**2b**) with phenethylamine gave the earlier unknown dimer **4b**, which is a thioanalog of chromenopyrimidine **4a** (Scheme 2).

It is important to note that the keeping a sample of **6** in DMSO-d$_6$ leads to the appearance of signals for the second compound, which turned to be identical to 2-(4-oxo-4*H*-thiochromen-3-yl)-5*H*-thiochromeno[2,3-*d*]pyrimidin-5-one (**4b**). A prolonged keeping at room temperature for 12 days, heating at 70—90 °C for 2 h, as well as addition of CF_3CO_2D, lead only to a somewhat (from 15 to 20%) increase in the content of dimer **4b**. A plausible mechanism of transformation **5** → **6** → **4b** is given in Scheme 3 and includes in the initial step (addition involving the amino group of one molecule at the benzylimino functional group of other molecule) formation of intermediate **A**, whose further intramolecular cyclization due to the elimination of one molecule of benzylamine as a result of 1,2-A$_N$ and S$_N$ reactions gives 1,5-diazocine **6**. This compound, being a diaminal, is capable of further partial recyclization to thermodynamically more stable thio-

Scheme 3



R = CH_2Ph, CH_2CH_2Ph

chromenopyrimidine **4b** through the intermediates **B**, **C**, **D**, and **E**. We assume that this process consists in the 8-membered ring opening to the intermediate **B** and 1,4-A_N-addition of the amino group at the enone fragment with the formation of spiro intermediate **C**, which further through pyrimidines **D** and **E** recyclizes to thiochromeno[2,3-*d*]pyrimidin-5-one **4b** with the loss of the second molecule of benzylamine (Scheme 3).

In the case of **2b** and phenethylamine, the initially formed chromone **5** with the phenethyl group at the imine nitrogen atom undergoes self-condensation to the intermediate **A**, which, omitting the step of formation of compound **6** (1,2-A_N), directly gives **B**. Further, intermediate **B** by the 1,4-A_N mechanism cyclizes to the intermediate **C**, which through **D** and **E** is transformed to dimer **4b**.

In the ^{1}H NMR spectrum of 1,5-diazocine **6** in DMSO-d_6, in addition to the signals of aromatic protons there are present signals for the NCH_2 group of AB-system (δ 3.64, $^2J_{AB}$ = 13.2 Hz), that reflects a chiral nature of compound **6**, and two two-proton doublets for the CH and NH groups at δ 5.34 and 9.52 ($^3J_{CH,NH}$ = 3.3 Hz), respectively. The structure of dimer **4b** was confirmed by the ^{1}H and ^{13}C NMR spectroscopic data, full assignment of all the signals was made based on analysis of the results of ^{1}H—^{13}C HSQC and HMBC 2D-experiments. The most informative are the following cross-peaks in the 2D HMBC spectrum in DMSO-d_6: H(2´)/C(3´), H(2´)/C(8a´), H(2´)/C(2), H(2´)/C(4´), H(4)/C(4a), H(4)/C(2), H(4)/C(10a), H(4)/C(5). The ^{1}H NMR spectrum of compound **4b** is characterized by a double set of signals for the aromatic protons, which are very close in chemical shifts and partially overlap, as a result, the doublets of doublets for the protons H(6) and H(5´) are found at δ 8.47 as a triplet of doublets with *J* = 8.0, 1.5 Hz. The signals for the protons H(2´) and H(4) are the most downfield and are observed at δ 9.07 and 9.59, respectively.

In conclusion, self-condensation of 3-cyanothiochromone upon the action of benzylamine or phenethylamine in boiling toluene leads to different products. In the first case, to the product of dimerization, 17-benzyl-6,7,14,15-tetrahydro-7,15-epiminobis(8*H*,16*H*-dithiochromeno)[2,3-*b*:2´,3´-*f*][1,5]diazocine-6,14-dione, while in the second, to 2-(thiochromon-3-yl)-5*H*-thiochromeno[2,3-*d*]pyrimidin-5-one.

Experimental

IR spectra were recorded on a Perkin—Elmer Spectrum BX-II spectrometer in KBr pellets and Bruker Alpha FTIR spectrometer with the appliance of disturbed total internal reflection (DTIR) (ZnSe crystal). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 and Bruker Avance II spectrometer in DMSO-d_6 (400 and 100 MHz, respectively) using Me_4Si as an internal standard. 3-Cyanothiochromone **2b** was obtained according to the known procedure.[3]

2-Amino-3-(benzyliminomethyl)thiochromone (5). A solution of thiochromone **2b** (150 mg, 0.8 mmol), benzylamine (85 mg, 0.8 mmol), and triethylamine (2 drops) in toluene (3 mL) was refluxed for 1 h. After the reaction mixture was cooled, a precipitate formed was filtered off, sequentially washed with toluene and diethyl ether, and dried. The yield was 170 mg (73%), a yellowish powder, m.p. 218—219 °C. IR, ν/cm^{-1}: 3236, 3210, 1615, 1590, 1576, 1527, 1509. Found (%): C, 68.94; H, 4.52; N, 9.22. $C_{17}H_{14}N_2OS$. Calculated (%): C, 69.36; H, 4.79; N, 9.52. ^{1}H NMR, δ: 4.73 (s, 2 H, CH_2); 7.24—7.38 (m, 5 H, Ph); 7.45—7.50 (m, 1 H, H(6)); 7.58—7.62 (m, 2 H, H(7), H(8)); 8.28 (d, 1 H, H(5), *J* = 7.7 Hz); 9.03 (s, 1 H, HC=N); 9.08 (br.s, 1 H, NH); 11.81 (br.s, 1 H, NH).

17-Benzyl-6,7,14,15-tetrahydro-7,15-epiminobis(8*H*,16*H*-dithiochromeno)[2,3-*b*:2´,3´-*f*][1,5]diazocine-6,14-dione (6). ***A.*** A solution of thiochromone **2b** (150 mg, 0.8 mmol), benzylamine (135 mg, 1.26 mmol), and triethylamine (4 drops) in toluene (3 mL) was refluxed for 14 h. After the reaction mixture was cooled, a precipitate formed was filtered off, sequentially washed with toluene and diethyl ether, and dried. The yield of the product was 72 mg (37%).

B. A solution of thiochromone **5** (150 mg, 0.51 mmol), benzylamine (55 mg, 0.51 mmol), and triethylamine (2 drops) in toluene (3 mL) was refluxed for 12 h. The treatment described in procedure *A* yielded compound **6** (35 mg, 28%). Colorless powder, m.p. 240—242 °C. IR (DTIR), ν/cm^{-1}: 3243, 3211, 1595, 1574, 1561, 1504. Found (%): C, 66.95; H, 3.63; N, 8.62. $C_{27}H_{19}N_3O_2S_2$. Calculated (%): C, 67.34; H, 3.98; N, 8.73. ^{1}H NMR, δ: 3.64 (AB-system, 2 H, CH_2, *J* = 13.2 Hz); 5.34 (d, 2 H, 2 CH, *J* = 3.3 Hz); 7.27—7.38 (m, 5 H, Ph); 7.46 (ddd, 2 H, 2 H(6), *J* = 8.0 Hz, *J* = 7.3 Hz, *J* = 1.2 Hz); 7.56 (td, 2 H, 2 H(7), *J* = 7.5 Hz, *J* = 1.5 Hz); 7.62 (dd, 2 H, 2 H(8), *J* = 8.0 Hz, *J* = 1.0 Hz); 8.24 (dd, 2 H, 2 H(5), *J* = 8.0 Hz, *J* = 1.5 Hz); 9.52 (d, 2 H, 2 NH, *J* = 3.3 Hz). ^{13}C NMR, δ: 53.1, 61.0, 106.2, 126.0, 126.8, 127.5, 128.4, 129.1, 129.4, 131.0, 132.2, 137.2, 153.4, 174.6.

2-(4-Oxo-4*H*-thiochromen-3-yl)-5*H*-thiochromeno[2,3-*d*]-pyrimidin-5-one (4b). A solution of thiochromone **2b** (150 mg, 0.8 mmol), phenethylamine (145 mg, 1.2 mmol), and triethylamine (4 drops) in toluene (3 mL) was refluxed for 10 h. After the reaction mixture was cooled, a precipitate formed was filtered off, washed with toluene, recrystallized from acetic acid, and dried. The yield was 37 mg (25%), yellow needle-like crystals, m.p. 248—250 °C. IR (DTIR), ν/cm^{-1}: 1633, 1587, 1547, 1510. Found (%): C, 63.83; H, 2.65; N, 7.46. $C_{20}H_{10}N_2O_2S_2$. Calculated (%): C, 64.15; H, 2.69; N, 7.48. ^{1}H NMR, δ: 7.69 (t, 1 H, H(6´), *J* = 7.5 Hz); 7.71 (t, 1 H, H(7), *J* = 7.5 Hz); 7.81 (td, 1 H, H(7´), *J* = 7.5 Hz, *J* = 1.2 Hz); 7.87 (td, 1 H, H(8), *J* = 7.5 Hz, *J* = 1.2 Hz); 7.94 (dd, 1 H, H(8´), *J* = 8.5 Hz); 7.96 (d, 1 H, H(9), *J* = 8.5 Hz); 8.46 (dd, 1 H, H(5´), *J* = 8.0 Hz, *J* = 1.5 Hz); 8.48 (dd, 1 H, H(6), *J* = 8.0 Hz, *J* = 1.5 Hz); 9.07 (s, 1 H, H(2´)); 9.59 (s, 1 H, H(4)). ^{13}C NMR, δ: 121.5 (C(4a)), 127.8 (C(8´)), 127.9 (C(9)), 128.4 (C(6´)), 128.8 (C(7)), 129.1 (C(5´)), 129.5 (C(6)), 129.9 (C(5a)), 132.6 (C(7´)), 132.9 (C(3´)), 133.1 (C(4a´)), 134.5 (C(8)), 135.8 (C(9a)), 136.5 (C(8a´)), 145.0 (C(2´)), 158.9 (C(4)), 164.8 (C(2)), 167.5 (C(10a)), 176.7 (C(4´)), 179.2 (C(5)).

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