Direct synthesis of 3-(diaminomethylidene)chromane-2,4-diones from 3-formylchromones and hydroxylamine

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3-(Diaminomethylidene)chromane-2,4-diones were synthesized from 4-oxo-4*H*-chromene-3-carbaldehyde and hydroxylamine in the presence of sodium hydroxide without isolation of intermediate products. Reflux of 3-(diaminomethylidene)chromane-2,4-dione in acetic anhydride gives rise to their monoacetyl derivatives at one of the amino groups.

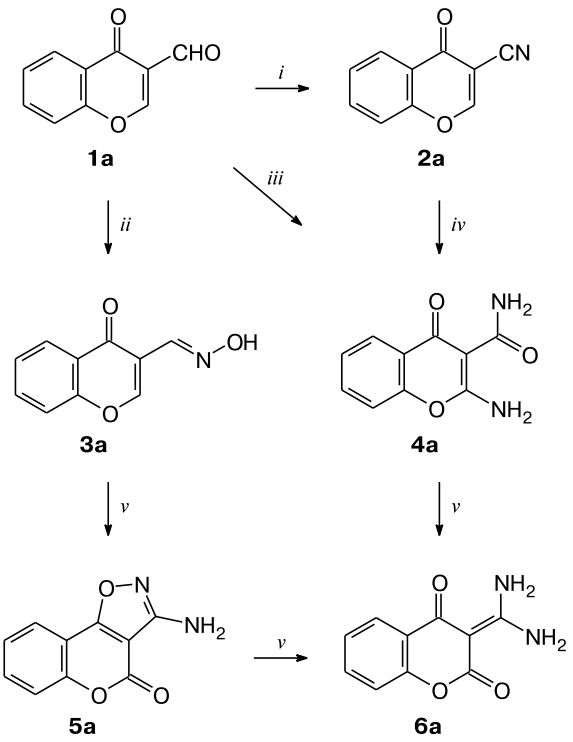
Key words: 4-oxo-4*H*-chromen-3-carbaldehydes, hydroxylamine, 3-(diaminomethylidene)chromane-2,4-diones, acetylation.

4-Oxo-4*H*-chromen-3-carbaldehyde (3-formylchromone) for a long time attracts attention of researchers as readily available and chemically highly active compound, which due to the presence of three electrophilic centers (C(2) and C(4) atoms, and 3-CHO group) serves as starting compound for the preparation of various heterocycles with a wide range of useful properties.[1,2] Reactions of 3-formylchromone with nucleophilic agents predominantly start from the attack on the unsubstituted C(2) atom and are accompanied by the pyrone ring opening, that leads to the arising of β-dicarbonyl intermediate capable of further intramolecular heterocyclizations.[3]

The reaction of 3-formylchromone (**1a**) with hydroxylamine is of special interest, because depending on the conditions it leads to the preparation of 3-cyanochromone (**2a**),[4] 3-formylchromone oxime (**3a**),[5] and 2-amino-3-carbamoylchromone (**4a**).[5,6] Recently, we have shown[6] that reflux of an ethanol solution of oxime **3a** with aqueous hydroxylamine hydrochloride in the presence of sodium hydroxide gives 3-amino-4*H*-chromeno[3,4-*d*]-isoxazol-4-one (**5a**), whereas 3-(diaminomethylidene)-chromane-2,4-dione (**6a**) is the final product in the reaction of chromone **1a** with hydroxylamine, which is formed from the intermediate compounds **4a** and **5a** under conditions for the transformation **3a** ⟶ **5a** (see Scheme 1).

Since the closest analogs of compound **6a** are 3-alkyl- or 3-(arylaminomethylidene)chromane-2,4-diones used for obtaining fused coumarins important from the medicinal point of view,[7,8] it was of interest to develop a direct synthesis of chromanediones **6a—c** from 3-formylchromone (**1a**), 6-methyl-3-formylchromone (**1b**), and 3-formyl-6-chlorochromone (**1c**), which would allow one to avoid the isolation step of the intermediate products **4** and **5**.

Scheme 1



Reagents and conditions: *i*. $NH_2OH \cdot HCl$, EtOH, HCl; *ii*. $NH_2OH \cdot HCl$, EtOH; *iii*. $NH_2OH \cdot HCl$, pyridine/H_2O (2 : 1); *iv*. $NH_2OH \cdot HCl$, AcONa, EtOH, H_2O; *v*. $NH_2OH \cdot HCl$, NaOH, EtOH, H_2O.

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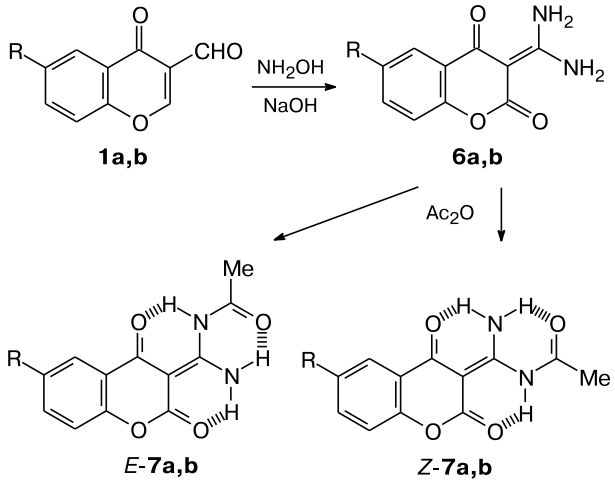
Results and Discussion

We found that chromane-2,4-diones **6a,b** are formed in 46—51% yields upon reflux of ethanol solutions of chromones **1a,b** (1 equiv.) with aqueous hydroxylamine hydrochloride (8 equiv.) in the presence of sodium hydroxide (14 equiv.) for 3 h (Scheme 2). It is important to note that no impurities of the intermediate compounds **4a,b** and **5a,b** were found in the reaction performed under these conditions by ^{1}H NMR spectroscopy and products **6a,b** were isolated in pure form without crystallization. A plausible mechanism of this unusual transformation includes a number of successive nucleophilic attacks by the hydroxylamine molecule, cyclization involving the phenol hydroxy group, and further reductive cleavage of the isoxazole ring of the intermediate **5** upon the action of hydroxylamine.[6]

Scheme 2



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

Reflux of chromanediones **6a,b** in acetic anhydride for 5 h gives monoacetyl derivatives **7a,b** in 45—55% yields, the ^{1}H NMR spectra of which, in addition to the signals for the aromatic protons, exhibit three slightly broadened singlets for the NH protons at δ 10.0, 10.8, and 13.9 and a singlet for the acetyl methyl group at δ 2.3. In both cases, compounds **7a,b** were formed as a single geometric isomer, however, no choice between *Z*- and *E*-isomers has been yet made.

The reaction of 6-chloro-3-formylchromone (**1c**) with an excess of hydroxylamine hydrochloride (8 equiv.) in the presence of an alkali furnishes a mixture of 3-(diaminomethylidene)-6-chlorochromane-2,4-dione (**6c**) and 2-amino-3-carbamoyl-6-chlorochromone (**4c**) of the composition **6c** : **4c** = 7 : 3, which is unseparable by crystallization. An increase in amount of hydroxylamine to 12 equiv. has no effect on the ratio of the products, rather leads only to their partial decomposition to 5-chlorosalicylic acid. Attempted synthesis of individual chromane-2,4-dione (**6c**) from 6-chloro-3-formylchromone oxime (**3c**) and a three-fold excess of hydroxylamine was not successful either: in this case, a mixture of chromane-2,4-dione **6c** and 3-amino-8-chloro-4*H*-chromeno[3,4-*d*]-isoxazole-4-one (**5c**) was isolated in the ratio 2 : 1, respectively.

In conclusion, we have developed a simple and efficient method for the synthesis of 3-(diaminomethylidene)chromane-2,4-diones from 3-formylchromones and hydroxylamine, that makes these compounds readily available for further study.

Experimental

IR spectra were recorded on a Perkin-Elmer Spectrum BX-II spectrometer in KBr pellets. ^{1}H, ^{13}C, and ^{15}N NMR spectra were recorded on a Bruker DRX-400 spectrometer in DMSO-d_6 (400.1, 100.6, and 40.5 MHz, respectively), using Me_4Si as an internal and liquid ammonia as an external standards. Chromones **1a—c** were obtained according to the known procedure.[9]

3-(Diaminomethylidene)chromane-2,4-dione (6a). A solution of hydroxylamine hydrochloride (5.1 g, 73.4 mmol) and sodium hydroxide (5.1 g, 128.0 mmol) in water was added to a solution of 3-formylchromone (**1a**) (1.6 g, 9.2 mmol) in ethanol (32 mL). The reaction mixture was refluxed for 3 h, cooled, and neutralized with 50% aqueous acetic acid to pH 6. The resulting solution was half concentrated and kept in a refrigerator for 5 h. A precipitate formed was filtered off, washed with 50% aq. acetic acid and water, then dried, and recrystallized from ethanol. The yield was 0.86 g (46%), brownish powder with m.p. 270—272 °C. Found (%): C, 57.39; H, 3.80; N, 13.04. $C_{10}H_8N_2O_3 \cdot 0.25H_2O$. Calculated (%): C, 57.56; H, 4.11; N, 13.42. IR, ν/cm^{-1}: 3429, 3290, 3157, 1684, 1633, 1610, 1568, 1487, 1473. ^{1}H NMR, δ: 7.28 (dd, 1 H, H(8); J = 8.2 Hz, 1.2 Hz); 7.30 (ddd, 1 H, H(6), J = 7.8 Hz, 7.3 Hz, 1.2 Hz); 7.63 (ddd, 1 H, H(7), J = 8.2 Hz, 7.3 Hz, 1.7 Hz); 7.69 (br.s, 2 H, NH_2); 7.94 (dd, 1 H, H(5), J = 7.8 Hz, 1.7 Hz); 9.82 (br.s, 2 H, NH_2). ^{13}C NMR, δ: 86.26 (C(3)), 116.22 (C(8)), 120.71 (C(4a)), 123.60 (C(6)), 125.44 (C(5)), 133.36 (C(7)), 152.46 (C(8a)), 163.93 (C(2)/C(3′)), 164.12 (C(3′)/C(2)), 177.96 (C4). ^{15}N NMR, δ: 94.2 (NH_2). MS (EI, 70 eV), m/z (I_{rel} (%)): 204 $[M]^+$ (100), 187 (19), 159 (13), 121 $[HOC_6H_4CO]^+$ (40), 120 $[OC_6H_4CO]^+$ (39), 109 (17), 92 $[C_6H_4O]^+$ (24), 84 (20), 68 (20), 65 (13), 64 (13), 63 (12).

3-(Diaminomethylidene)-6-methylchromane-2,4-dione (6b) was obtained from **1b** similarly to compound **6a**, the yield was 51%, slightly yellowish powder with m.p. ~315 °C (with decomp.). Found (%): C, 60.27; H, 4.43; N, 12.82. $C_{11}H_{10}N_2O_3$. Calculated (%): C, 60.55; H, 4.62; N, 12.84. IR, ν/cm^{-1}: 3359, 3107, 1671, 1624, 1607, 1578, 1489. ^{1}H NMR, δ: 2.36 (s, 3 H, Me); 7.16 (d, 1 H, H(8), J = 8.3 Hz); 7.42 (ddq, 1 H, H(7), J = 8.3 Hz, 2.3 Hz, 0.6 Hz); 7.67 (br.s, 2 H, NH_2); 7.72 (dq, 1 H, H(5), J = 2.3 Hz, 0.6 Hz); 9.82 (br.s, 2 H, NH_2).

Mixture of 3-(diaminomethylidene)-6-chlorochromane-2,4-dione (6c) and 3-amino-8-chloro-4*H*-chromeno[3,4-*d*]isoxazol-4-one (5c). This mixture was obtained in total yield of 15% from oxime **3c**, $NH_2OH \cdot HCl$ (3 equiv.), and NaOH (5 equiv.) according to the procedure described earlier.[5] ^{1}H NMR of compound **6c** (67%), δ: 7.34 (d, 1 H, H(8), J = 8.8 Hz); 7.66 (dd, 1 H, H(7), J = 8.8 Hz, 2.7 Hz); 7.73 (br.s, 2 H, NH_2); 7.84 (d, 1 H, H(5), J = 2.7 Hz); 9.70 (br.s, 2 H, NH_2); of compound **5c** (33%), δ: 6.49 (s, 2 H, NH_2); 7.62 (d, 1 H, H(6), J = 9.0 Hz); 7.81 (dd, 1 H, H(7), J = 9.0 Hz, 2.6 Hz); 8.08 (d, 1 H, H(9), J = 2.6 Hz).

A mixture of 3-(diaminomethylidene)-6-chlorochromane-2,4-dione (**6c**) and 2-amino-3-carbamoyl-6-chlorochromone (**4c**)[10] of the composition **6c** : **4c** = 7 : 3 was obtained from chromone **1c** under conditions described for chromanedione **6a** in total yield of 35%.

***N*-Acetyl-3-(diaminomethylidene)chromane-2,4-dione (7a).** A solution of chromanedione **6a** (250 mg, 1.22 mmol) in acetic anhydride (3 mL) was refluxed for 5 h, cooled, and kept for 16 h. A precipitate formed was filtered off, washed with acetic acid, and dried. The yield was 45%, brownish needle-like crystals with m.p. 181—182 °C. Found (%): C, 58.58; H, 3.88; N, 11.24. $C_{12}H_{10}N_2O_4$. Calculated (%): C, 58.54; H, 4.09; N, 11.38. IR, ν/cm^{-1}: 3330, 3212, 1712, 1687, 1635, 1611, 1548. ^{1}H NMR, δ: 2.31 (s, 3 H, Me); 7.34—7.39 (m, 2 H, H(8), H(6)); 7.70 (ddd, 1 H, H(7), J = 8.3 Hz, 7.3 Hz, 1.7 Hz), 7.97 (dd, 1 H, H(5), J = 7.8 Hz, 1.7 Hz); 10.04, 10.82, 13.85 (all br.s, 1 H, NH).

***N*-Acetyl-3-(diaminomethylidene)-6-methylchromane-2,4-dione (7b)** was obtained similarly to compound **7a**, the yield was 55%, brownish powder with m.p. 183—184 °C. Found (%): C, 59.70; H, 4.45; N, 10.62. $C_{13}H_{12}N_2O_4$. Calculated (%): C, 60.00; H, 4.65; N, 10.76. IR, ν/cm^{-1}: 3334, 3204, 1706, 1685, 1634, 1609, 1566, 1536, 1492. ^{1}H NMR, δ: 2.31, 2.37 (both s, 3 H, Me); 7.24 (d, 1 H, H(8), J = 8.4 Hz); 7.50 (dd, 1 H, H(7), J = 8.4 Hz, 2.0 Hz), 7.75 (d, 1 H, H(5), J = 2.0 Hz); 10.02, 10.85, 13.86 (all br.s, 1 H, NH).

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