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Ring transformation of chromone-3-carboxamide

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ABSTRACT

4-Hydroxycoumarin-3-carboxaldehyde (**5**) was obtained from chromone-3-carboxaldehyde (**1**) via chromone-3-carboxamide (**2**) and 3-aminomethylene-2*H*-chroman-2,4-dione (**3**). 3-Alkylaminomethylenechroman-2,4-diones (**7**,**8**) were obtained from the reaction of primary aliphatic amines with chromone-3-carboxamide (**2**). Treatment of chromone-3-carboxamide with sodium methoxide gives 3-(2-hydroxybenzoyl)-2*H*-chromeno[2,3-*b*]pyridine-2,5(1*H*)-dione (**9**).

1. Introduction

Chromone derivatives have received considerable attention due to their medicinal activities[1] and they can be converted to a broad range of heterocyclic systems through reactions with nucleophiles.[2] Several reports describe the action of different nucleophiles on various 3-substituted chromones. The structures of the products obtained depend on the substituents at the 3-position and the reaction conditions. New derivatives of 3-(2-hydroxybenzoyl)-1*H*-pyrroles were obtained from the reaction of chromone-3-carboxaldehyde with hetarylmethylamines and glycine derivatives.[3] Piperidine undergoes 1,4-addition to chromone-3-carboxaldehyde with subsequent deformylation giving rise to 1-(2-hydroxyphenyl)-3-piperidin-1-yl propenone.[4] Reaction of chromone-3-carboxaldehyde with active methylene compounds in the presence of ammonia gives 5-(2-hydroxybenzoyl)pyridines.[5] Chromone-3-carboxaldehyde-oxime and chromone-3-carbonitrile on treatment with aqueous sodium hydroxide solution afforded 2-aminochromone-3-carboxaldehyde.[6] Furthermore, heating chromone-3-carboxylate with concentrated ammonium hydroxide leads to 3-formimidoyl-4-hydroxycoumarin.[7] Primary and secondary amines reacted with 3-bromochromone to yield ring contraction products and 3-aminochromones.[8] As an extension of work in the area of 3-substituted chromones, the present investigation describes the action of bases (NH_4OH, NaOH, RNH_2 and sodium methoxide) on chromone-3-carboxamide (**2**).

2. Results and discussion

Chromone-3-carboxamide (**2**) was prepared previously from chromone-3-carboxaldehyde (**1**) via conversion to the corresponding carboxylic acid using *Jones*' reagent (22% yield), followed by transformation to the acid chloride and subsequently to the amide by reaction with ammonia.[9] In contrast to this difficult method, chromone-3-carboxamide (**2**) was prepared easily using an elegant method which relied upon the feasibility of oxidation of chromone-3-carboxaldehyde (**1**) using *N*-bromosuccinamide (NBS) followed by quenching with ammonia in a one step synthesis. Based on the photo-induced NBS oxidation of some aldehydes by Cheung,[10] herein we disclose our present successful results. Treatment of a suspension of carboxaldehyde **1** in CCl_4 with 1.2 mol equiv of NBS under irradiation using a 200 W Tungsten lamp for 40 min afforded, after quenching with ammonia at 0 °C, chromone-3-carboxamide (**2**) in one pot (Scheme 1). The structure of compound **2** was deduced from its elemental analysis and spectral data. The IR spectrum of **2** displayed characteristic absorption bands at 3364, 3284 (NH_2), 1682 ($C{=}O_{amide}$) and 1615 ($C{=}O_{pyrone}$) cm^{-1}. Its ^1H NMR spectrum showed two characteristic singlet signals at δ 8.53 (NH_2 exchangeable with D_2O) and 9.03 (H-2).

In another experiment, quenching the reaction product of chromone-3-carboxaldehyde (**1**) and NBS with an excess of ammonia at room temperature (40 °C) afforded 3-aminomethylene-2*H*-chroman-2,4-dione (**3**) (Scheme 1) which was erroneously reported by Klutchko[7] as 3-formamidoyl-4-hydroxycoumarin. ^1H NMR spectrum of compound **3** displayed a characteristic triplet at δ 8.39 for the vinyl proton. In addition, compound **3** was also obtained when carboxamide **2** was allowed to react with concentrated ammonium hydroxide at room temperature (40 °C). This result supports the

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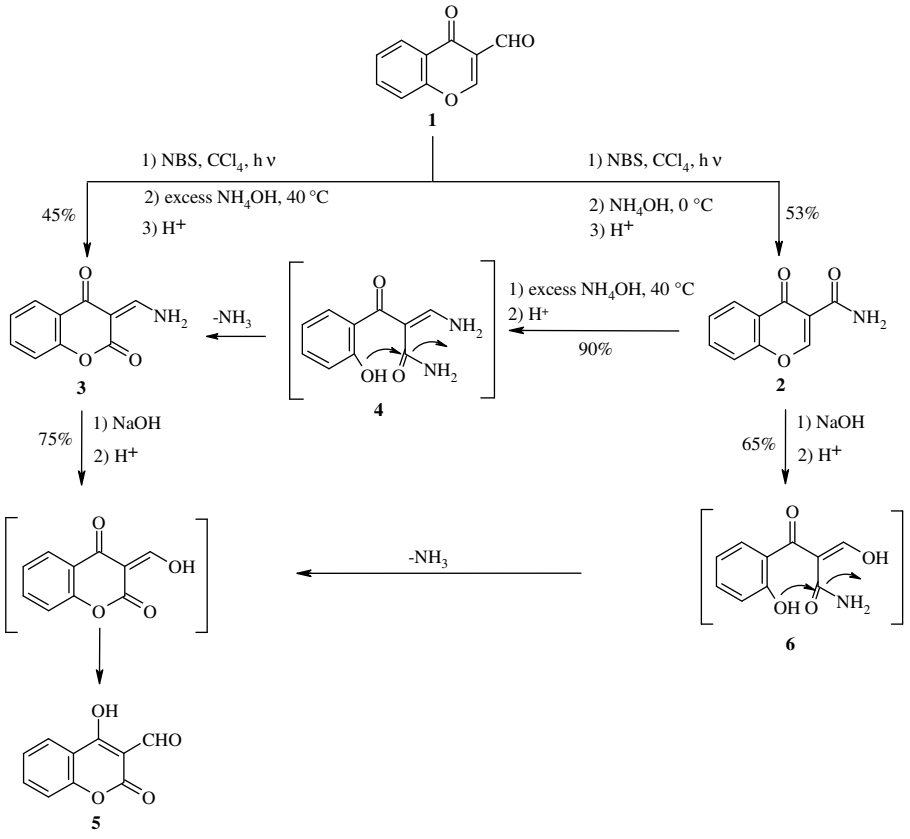


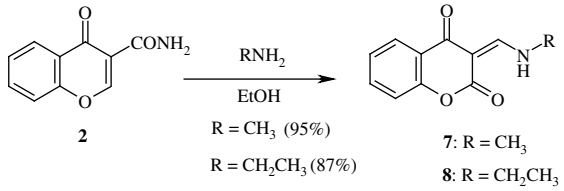
Scheme 1. Conversion of chromone-3-carboxaldehyde (**1**) to 4-hydroxycoumarin-3-carboxaldehyde (**5**).

postulated mechanism for the formation of enaminone **3** from carboxaldehyde **1** which may proceed through the formation of the corresponding amide which undergoes direct ring opening under the influence of ammonia followed by ring closing (RORC) through lactonization of intermediate **4** with loss of one molecule of ammonia (Scheme 1).

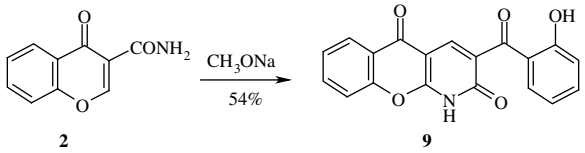
Treatment of carboxamide **2** with aqueous 1 M NaOH solution resulted in the facile rearrangement to the known 4-hydroxycoumarin-3-carboxaldehyde (**5**).[11] The reaction may proceed through RORC through lactonization of the postulated intermediate **6**. The same conversion was also observed when enaminone **3** was treated with 1 M NaOH solution under the same conditions (Scheme 1).

Ghosh[12] has reported that 3-(alkyl-/arylaminomethylene)chroman-2,4-diones are considered as very good precursors for the synthesis of various heterocycles fused at the 3,4-position of a 1-benzopyran and may be a synthetic equivalent of the versatile substrate 4-hydroxycoumarin-3-carboxaldehyde (**5**). Therefore, 3-(methyl-/ethylaminomethylene) chroman-2,4-diones (**7** and **8**) were prepared by refluxing an ethanolic solution of **2** with methyl- or ethyl amine for 15 min, respectively (Scheme 2). This new preparation of **7** and **8** involved a short reaction time, easy work-up and was devoid of any chromatographic separation producing single geometrical isomeric products. These are expected to be *E* isomers and showed low δ values for the NH protons and higher stretching absorption values for the OC═O groups compared to the *Z* isomers.[13] The structures of compounds **7** and **8** were established from their IR and ^{1}H NMR spectra. The formation of **7** and **8** may proceed through a mechanism similar to that depicted in Scheme 1. According to our knowledge this is the only method for the preparation of 3-(alkylaminomethylene)chroman-2,4-diones (**7**,**8**) as pure isomers. These compounds were obtained previously as mixtures of *Z* and *E* isomers together with 2-alkylamino-3-formylchromone via rearrangement of *C*-(chromon-3-yl)-*N*-alkylnitrones in refluxing xylene.[14]

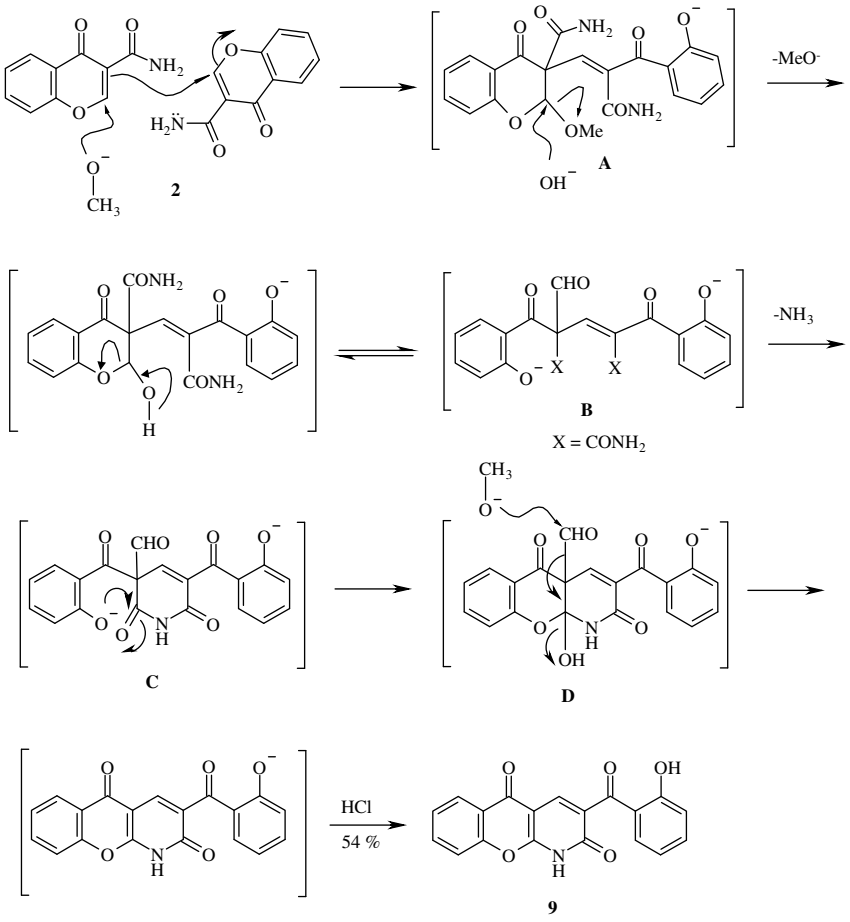
A new derivative of heteroannulated chromone, namely 3-(2-hydroxybenzoyl)-2*H*-chromeno[2,3-*b*]pyridine-2,5(1*H*)-dione (**9**) was obtained from the reaction of chromone-3-carboxamide (**2**) with sodium methoxide solution (Scheme 3). The suggested mechanism for the formation of compound **9,** as depicted in Scheme 4, proceeds through methoxide catalysed ring-ring addition in which two consecutive *Michael* additions gave the intermediate **A**. The intermediate **A** underwent ring opening via nucleophilic attack of hydroxide ion at the acetal carbon giving rise to the aldehyde intermediate **B** which in turn be heterocyclized via loss of ammonia to give the imide intermediate **C**. Intramolecular



Scheme 2. Synthesis of enaminones **7** and **8**.



Scheme 3. Formation of annulated chromone **9**.



Scheme 4. The proposed mechanism for the formation of compound **9**.

ring closure of the imide **C** was conducted by attack of the phenolate oxygen at the α-carbon giving chromenopyridine **D** and deformylation led to formation of the product **9**.[15]

3. Experimental

3.1. General

All melting points are uncorrected and were recorded in open capillary tubes on Stuart SMP3 melting point apparatus. Infrared spectra were recorded on FT-IR Bruker Vector 22 spectrophotometer using KBr wafer technique. ^{1}H NMR spectra (chemical shift in δ) were measured on Gemini spectrometer 200 MHz using DMSO-d_6 as solvent and TMS as an internal standard. Elemental microanalyses were performed at the Cairo University Microanalytical Center. Chromone-3-carboxaldehyde (**1**) was prepared by Vilsemier–Haack double formylation according to the published method by Nohara.[16]

3.2. Chromone-3-carboxamide (2)

A mixture of chromone-3-carboxaldehyde (**1**) (1.74 g, 10 mmol) and NBS (2.14 g, 12 mmol) in CCl_4 (100 mL) was stirred under irradiation from a 200 W Tungsten lamp for 40 min. The solvent was evaporated under vacuum and the residue was cooled in an ice bath followed by addition of concentrated ammonium hydroxide (3 mL) with continuous stirring. The reaction mixture was neutralized with 5% acetic acid. The solid obtained was filtered, washed with water and crystallized from ethanol to give **2** as white crystals, mp 251–252 °C (lit.[9] 250–252 °C), yield (1 g, 53%). Anal. Calcd for $C_{10}H_7NO_3$ (189.17): C, 63.49; H, 3.73; N, 7.40%. Found: C, 63.16; H, 3.71; N, 7.54%. IR (KBr, cm^{-1}): 3364, 3284 (NH_2), 3061 ($CH_{arom.}$), 1682 ($C{=}O_{amide}$), 1615 ($C{=}O_{pyrone}$). ^{1}H NMR (DMSO-d_6, δ): 7.56 (t, J=7 Hz, 1H, H_6), 7.63 (d, J=6.8 Hz, 1H, H_8), 7.93 (t, J=6.8 Hz, 1H, H_7), 8.21 (d, J=7 Hz, 1H, H_5), 8.53 (br s, 2H, NH_2 exchangeable with D_2O), 9.03 (s, 1H, H-2).

3.3. 3-Aminomethylene-2*H*-chroman-2,4-dione (3)

*3.3.1. From chromone-3-carboxaldehyde (**1**)*

A mixture of **1** (1.74 g, 10 mmol) and NBS (2.14 g, 12 mmol) in CCl_4 (100 mL) was stirred under irradiation from a 200 W Tungsten lamp for 40 min. The solvent was evaporated under vacuum and the residue was cooled to room temperature followed by addition of concentrated ammonium hydroxide (8 mL) with continuous stirring. The reaction mixture was neutralized with 5% acetic acid. The solid obtained was filtered, washed with water and crystallized from ethanol to give **3** as white crystals, mp 240–241 °C, yield (0.85 g, 45%).

*3.3.2. From chromone-3-carboxamide (**2**)*

A mixture of **2** (0.189 g, 1 mmol) and concentrated ammonium hydroxide (2 mL) was stirred at 40 °C for 30 min, after cooling to room temperature the reaction mixture was diluted with water (5 mL) and neutralized with 5% acetic acid. The solid obtained was filtered, washed with water and crystallized from ethanol to give **3** as white crystals, mp 240–241 °C, yield (0.17 g, 90%). Anal. Calcd for $C_{10}H_7NO_3$ (189.17): C, 63.49; H, 3.73; N, 7.40%. Found: C, 62.96; H,

3.70; N, 7.37%. IR (KBr, cm^{-1}): 3277, 3128 (NH_2), 1694 (C=$O_{lactone}$), 1630 (C=$O_{enaminone}$). ^1H NMR (DMSO-d_6, δ): 7.26–7.35 (m, 2H, H_6 and H_8), 7.65 (t, J=7.2 Hz, 1H, H_7), 7.93 (d, J=7.4 Hz, 1H, H_5), 8.39 (t, 1H, =*CH*), 9.85 (br s, 1H, 1H of NH_2 exchangeable with D_2O), 10.85 (br s, 1H, 1H of NH_2 exchangeable with D_2O).

3.4. 4-Hydroxycoumarin-3-carboxaldehyde (5)

A mixture of **2** and/or **3** (0.189 g, 1 mmol) and 1 M aqueous sodium hydroxide solution (10 mL) was stirred overnight at room temperature followed by neutralization with 5% acetic acid. The solid obtained was filtered and crystallized from petroleum ether 60–80 to give **5** as white crystals, mp 135–137 °C (lit.[11] 136–137). Anal. Calcd for $C_{10}H_6O_4$ (190.16): C, 63.16; H, 3.18%. Found: C, 63.88; H, 3.20%. IR (KBr, cm^{-1}): 3436 (OH), 3078 ($CH_{arom.}$), 1733 (C=$O_{lactone}$), 1675 (C=$O_{ald.}$). ^1H NMR (DMSO-d_6, δ): 7.39–7.47 (m, 2H, H_6 and H_8), 7.82 (t, J=7.6 Hz, 1H, H_7), 8.02 (d, J=8.2 Hz, 1H, H_5), 9.87 (s, 1H, CHO).

3.5. 3-Methylaminomethylenechroman-2,4-dione (7)

A mixture of chromone-3-carboxamide (**2**) (0.189 g, 1 mmol) and aqueous methyl amine (0.26 mL, 3 mmol, 36% w/v) in ethanol (5 mL) was heated on a water bath with continuous stirring for 15 min. After cooling, the yellow crystals obtained were filtered and recrystallized from methanol to give **7** as white crystals, mp 204–205 °C, yield (0.18 g, 95%). Anal. Calcd for $C_{11}H_9NO_3$ (203.20): C, 65.02; H, 4.46; N, 6.89%. Found: C, 64.95; H, 4.40; N, 6.91%. IR (KBr, cm^{-1}): 3177 (NH), 3040 ($CH_{arom.}$), 2987, 2950 (CH_3), 1721 (C=$O_{lactone}$), 1629 (C=$O_{enaminone}$). ^1H NMR (DMSO-d_6, δ): 3.30 (s, 3H, CH_3), 7.26–7.35 (m, 2H, H_6 and H_8), 7.62 (t, J=7 Hz, 1H, H_7), 7.93 (d, J=7.8 Hz, 1H, H_5), 8.50 (d, 1H, =*CH*), 11.45 (br s, 1H, NH).

3.6. 3-Ethylaminomethylenechroman-2,4-dione (8)

A mixture of chromone-3-carboxamide (**2**) (0.189 g, 1 mmol) and aqueous ethyl amine (0.19 mL, 3 mmol, 70% w/v) in ethanol (5 mL) was heated on a water bath with continuous stirring for 15 min. After cooling, the white crystals obtained were filtered and recrystallized from methanol to give **8** as white crystals, mp 184 °C, yield (0.18 g, 87%). Anal. Calcd for $C_{12}H_{11}NO_3$ (217.23):C, 66.35; H, 5.10; N, 6.45%. Found: C, 66.44; H, 5.42; N, 6.25%. IR (KBr, cm^{-1}): 3181 (NH), 3080 ($CH_{arom.}$), 2969, 2932, 2872 (CH_2 and CH_3), 1705 (C=$O_{lactone}$), 1640 (C=$O_{enaminone}$). ^1H NMR (DMSO-d_6, δ): 1.27 (t, J=7 Hz, 3H, CH_3), 3.64 (q, J=7 Hz, 2H, CH_2), 7.32 (m, 2H, H_6 and H_8), 7.66 (t, J=7.3 Hz, 1H, H_7), 7.94 (d, J=7.2 Hz, 1H, H_5), 8.47 (d, 1H, =*CH*), 11.66 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ): 15.2 (CH_3), 43.6 (CH_2), 98.2 (C-3), 120.4 (C-8), 123.1 (C-6), 124.3 (C-4a), 126.4 (C-7), 134.8 (C-5), 145.0 (C vinyl), 149.8 (C-8a), 162.7 (C-2 as OC=O), 181.8 (C-4 as C=O).

3.7. 3-(2-Hydroxybenzoyl)-2*H*-chromeno[2,3-*b*]pyridine-2,5(1*H*)-dione (9)

A mixture of **2** (0.189 g, 1 mmol) and sodium methoxide (prepared by dissolving 0.1 g sodium in 20 mL methanol) was refluxed for 2 h. The reaction mixture was neutralized with dilute HCl. The solid obtained was filtered and crystallized from dioxane to give **9** as yellow crystals, yield (0.09 g, 54%), mp 275 °C. Anal. Calcd for $C_{19}H_{11}NO_5$ (333.30): C, 68.47; H, 3.33; N, 4.20%. Found: C, 68.35; H, 3.54; N, 3.91%. IR (KBr, cm^{-1}): 3448 (OH), 3365 (NH), 3085 ($CH_{arom.}$), 1648 and 1630 (3C=O). ^1H NMR (DMSO-d_6, δ): 6.95 (t, 2H, Ar–H), 7.45–7.79 (m, 5H, Ar–H), 8.17 (s, 1H, H-$4_{pyridine}$), 8.62 (d, J=7.2 Hz, 1H, H-6), 10.88 (br s, 1H, NH exchangeable with D_2O), 13.03 (br s, 1H, OH exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, δ): 108.2 (C-4a), 114.3 (C-9), 118.9 (C-3′), 119.4 (C-5a), 120.9 (C-5′), 124.6 (C-1′), 125.9 (C-6), 126.7 (C-7), 132.6 (C-3), 133.4 (C-4′), 135.9 (C-8), 137.3 (C-6′), 140.4 (C-4), 149.2 (C-9a), 154.8 (C-2′), 160.8 (C-10a), 161.2 (C-2 as C=O), 163.1 (C-5 as C=O), 196.5 (C=O_{ketone}). MS (m/z, %): 333 (M^+, 100), 316 (35), 313 (59), 240 (45), 213 (59), 121 (63) and 93 (25).

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