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Synthesis and chemical reactivity of the novel 6,8-dibromo-7-hydroxychromone-3-carboxaldehyde

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Abstract

A novel 6,8-dibromo-7-hydroxychromone-3-carboxaldehyde (**4**) was prepared from the Vilsemier-Haack formylation of 3,5-dibromo-2,4-dihydroxyacetophenone (**3**). The chemical reactivity of carboxaldehyde **4** was studied towards some hydrazine derivatives under different reaction conditions. 1,3,4-Thiadiazol-2-ylchromone derivative **10** was also prepared. The chemical behavior of carboxaldehyde **4** was studied towards hydroxylmine hydrochloride under different reaction conditions to produce compounds **11**-**14**. The reaction mechanisms and mass spectrometry for some compounds were also reported.

Keywords: chromone-3-carboxaldehyde, nucleophilic reactions, ring opening ring closure reactions, mass spectrometry.

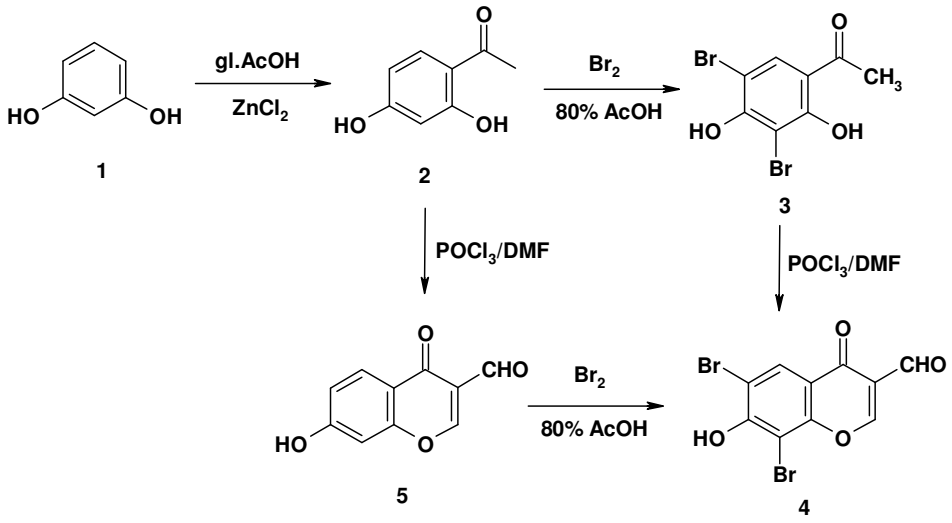
Introduction

Chromones have attracted attention from the point of view of both biological activity [1-3] and organic synthesis [4]. Chromone derivatives have been found to exhibit a broad range of biological activities, including antifungal, antiviral, antimicrobial, antiallergenic, anticonvulsant and antitumor activity [5-8]. These derivatives also serve as intermediates to many products of fine chemical industries such as pharmaceuticals, agrochemicals and dyestuffs [9,10]. Among the different functionalized chromones, 3-formylchromones occupy a unique position because they can be transformed into various heterocycles by interesting reactions with different nucleophiles [11-13]. 3-Formylchromones occupy an important position in the synthesis

of various heterocyclic systems due to the availability of three electron deficient sites, C-2, the aldehyde carbon and the C-4 of the carbonyl group. Moreover, 3-formylchromones are a versatile synthons for the synthesis of a variety of novel heterocyclic systems possessing diverse biological activities [14]. In continuation to our aforementioned word on the chemistry of 3-substituted chromones [15-19], the present work aims at the synthesize of the novel 6,8-dibromo-7-hydroxychromone-3-carboxaldehyde and study its chemical reactivity towards some hydrazines and hydroxylamine hydrochloride under different reaction conditions.

Results and Discussion

Acetylation of resorcinol (**1**) using the standard procedure [20] gave 2,4-dihydroxyacetophone (**2**) [resacetophenone] which on bromination using bromine in 80% AcOH afforded 3,5-dibromo-2,4-dihydroxyacetophenone (**3**) [21]. Vilsemier–Haack formylation of the latter compound produced the novel 6,8-dibromo-7-hydroxychromone-3-carboxaldehyde (**4**) [22]. Compound **4** was also obtained *via* Vilsemier–Haack formylation of 2,4-dihydroxyacetophenone (**2**) to produce 7-hydroxychromone-3-carboxaldehyde (**5**) [23] which upon bromination afforded the target compound **4** (Scheme 1). Structure of carboxaldehyde **4** was deduced from its correct elemental analysis and spectral data. The IR spectrum of compound **4** showed two characteristic absorption bands at 1685 and 1667 cm^{-1} attributed to $C=O_{ald.}$ and $C=O_{\gamma\text{-pyrone}}$, respectively. Its ^{1}H-NMR spectrum consists of three singlet signals at δ 8.16, 8.89 and 10.07 ppm due to H-5, H-2 and aldehyde proton, respectively. The mass spectrum of compound **4** showed the molecular ion peak at m/z 346, and the base peak at m/z 320. In addition, the relative intensity of M, M+2 and M+4 in the ratio 1: 2: 1 as expected for compounds contains two bromine atoms. This ratio retain during the fragmentation pattern when the fragment contains the two bromine atoms. While, after loss of one bromine atom during fragmentation, the relative intensity of M: M+2 changed to 1:1. The mass fragmentation pattern of carboxaldehyde **4** is depicted is Figure 1.



Scheme 1. Synthesis of 6,8-dibromo-7-hydroxychromone-3-carboxaldehyde (**4**).

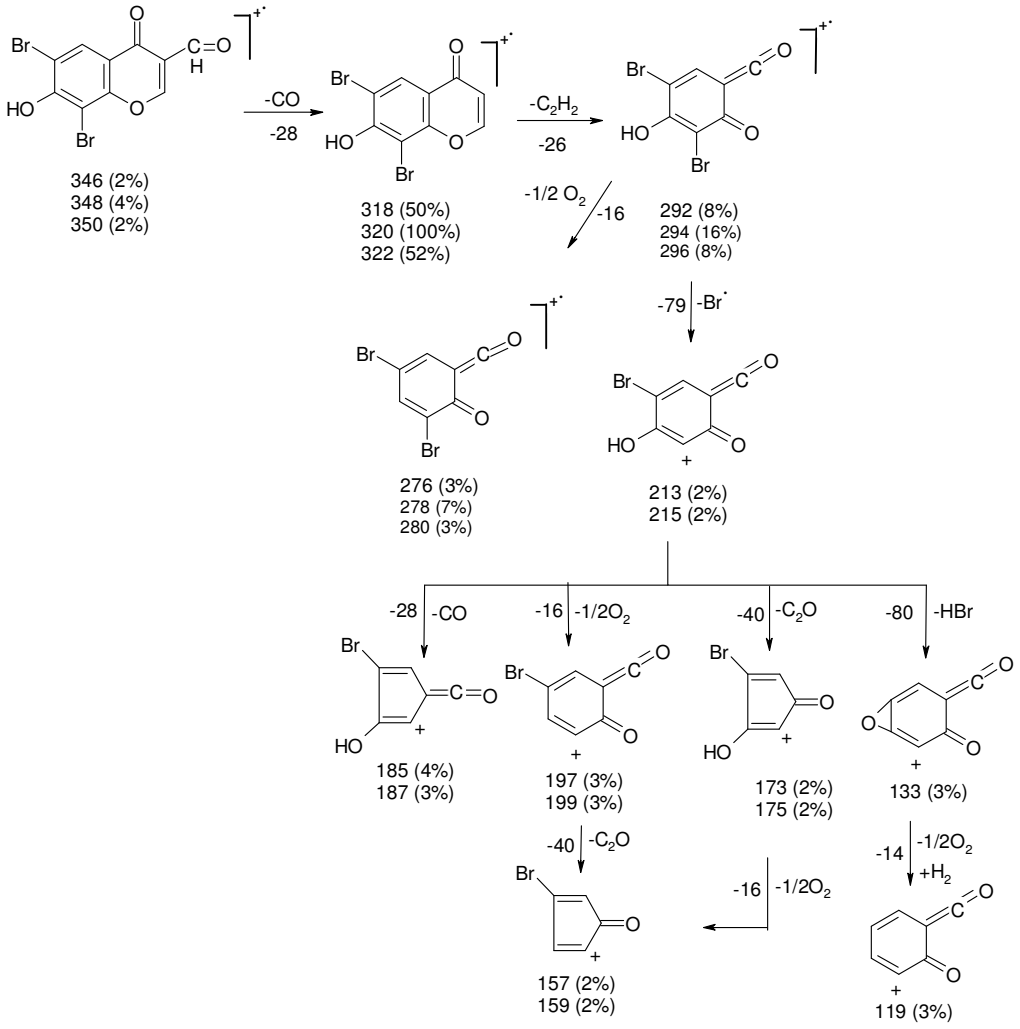
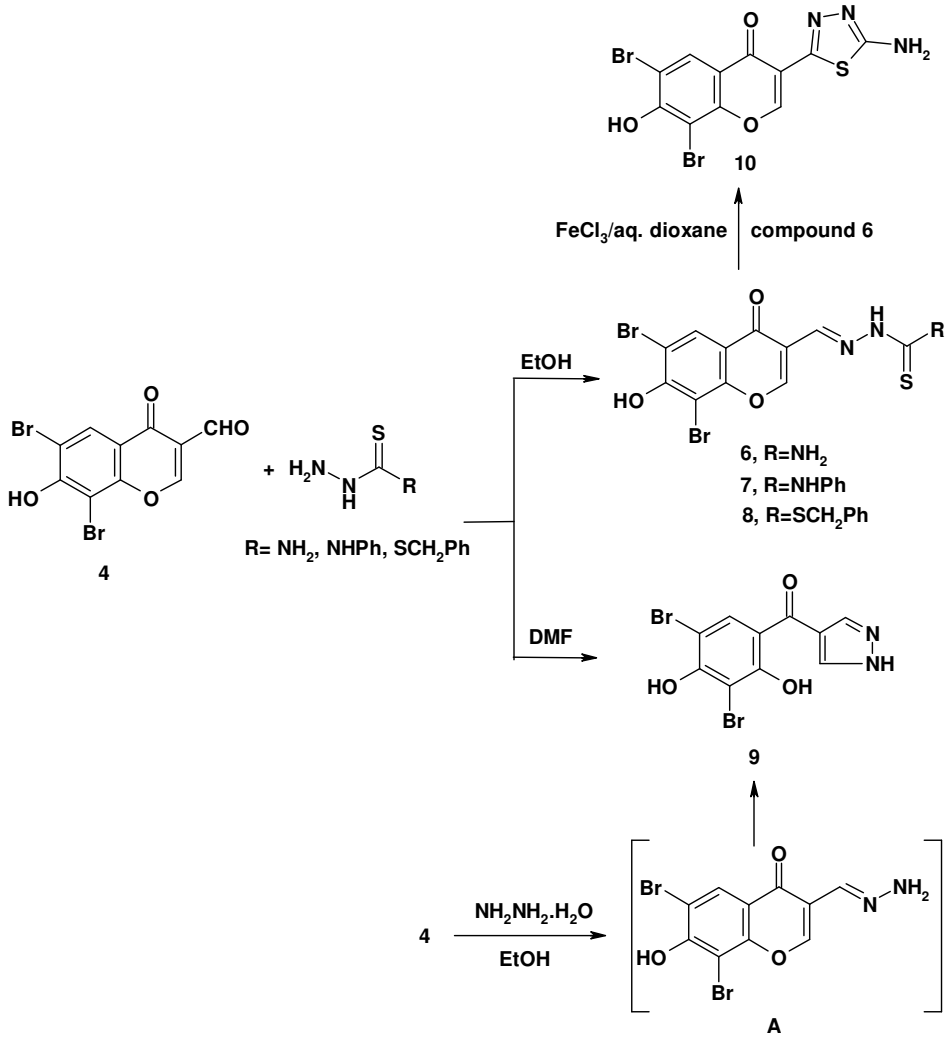


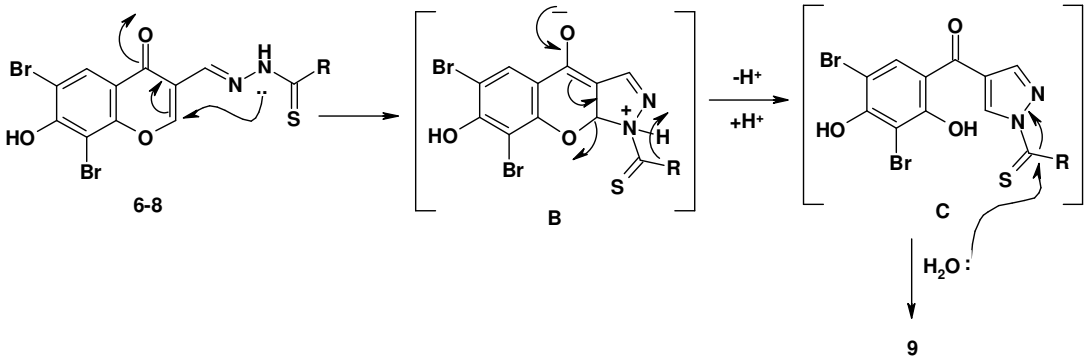
Figure 1. The mass fragmentation pattern of carboxaldehyde **4**.

Condensation of carboxaldehyde **4** with thiosemicarbazide, N^4-phenylthiosemicarbazide and *S*-benzyl dithiocarbazate, in boiling ethanol afforded the corresponding hydrazone derivatives **6**-**8**, respectively. while when the latter reactions take place in boiling DMF, only one product **9** was isolated, in all cases, which was identified as (3,5-dibromo-2,4-dihydroxybenzoyl)-1*H*-pyrazole (**9**) (Scheme 2). The pyrazole derivative **9** was obtained authentically (the same mp and mmp and spectral data) from the condensation of carboxaldehyde **4** with hydrazine hydrate in absolute ethanol, *via* the non isolable hydrazone intermediate **A** (Scheme 2).



Scheme 2. Condensation of carboxaldehyde **4** with hydrazine derivatives.

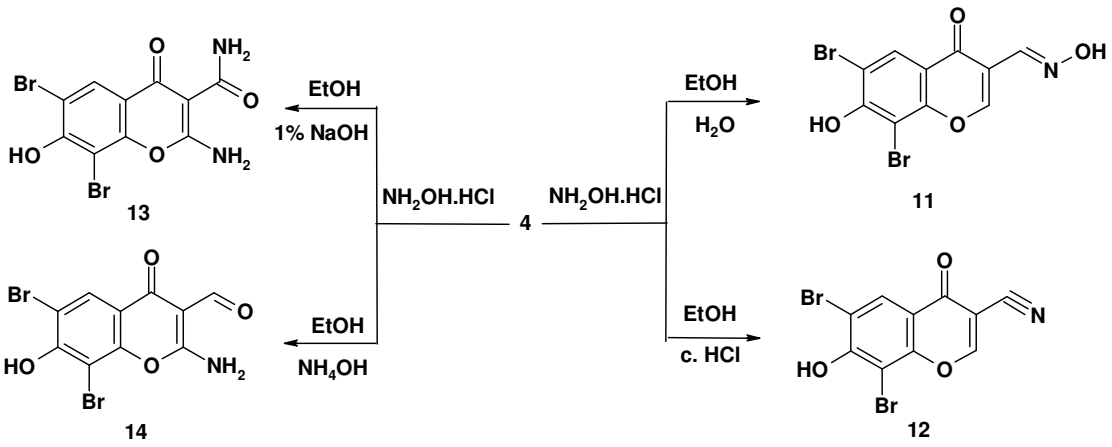
Formation of pyrazole derivative **9**, in boiling DMF) may occur *via* the formation of hydrazones **6**-**8** followed by intermolecular nucleophilic addition at C-2 position, intermediates **B**, with concomitant γ-pyrone ring opening to afford intermediates **C**, which underwent heterolytic cleavage of the thioamidic bonds to produce the pyrazole derivative **9**. The proposed mechanism for the formation of pyrazole derivative **9** is depicted in Scheme 3 [24]. The ^{1}H-NMR spectrum of pyrazole **9** showed three characteristic singlet signals at δ 7.84, 8.32 and 8.59 ppm assigned to CH_{arom}, $H_{5\ pyrazole}$ and $H_{3\ pyrazole}$, respectively. The mass spectrum of pyrazole **9** showed the molecular ion peak at m/z 360.



Scheme 3. The proposed mechanism for the formation of pyrazole derivative **9**.

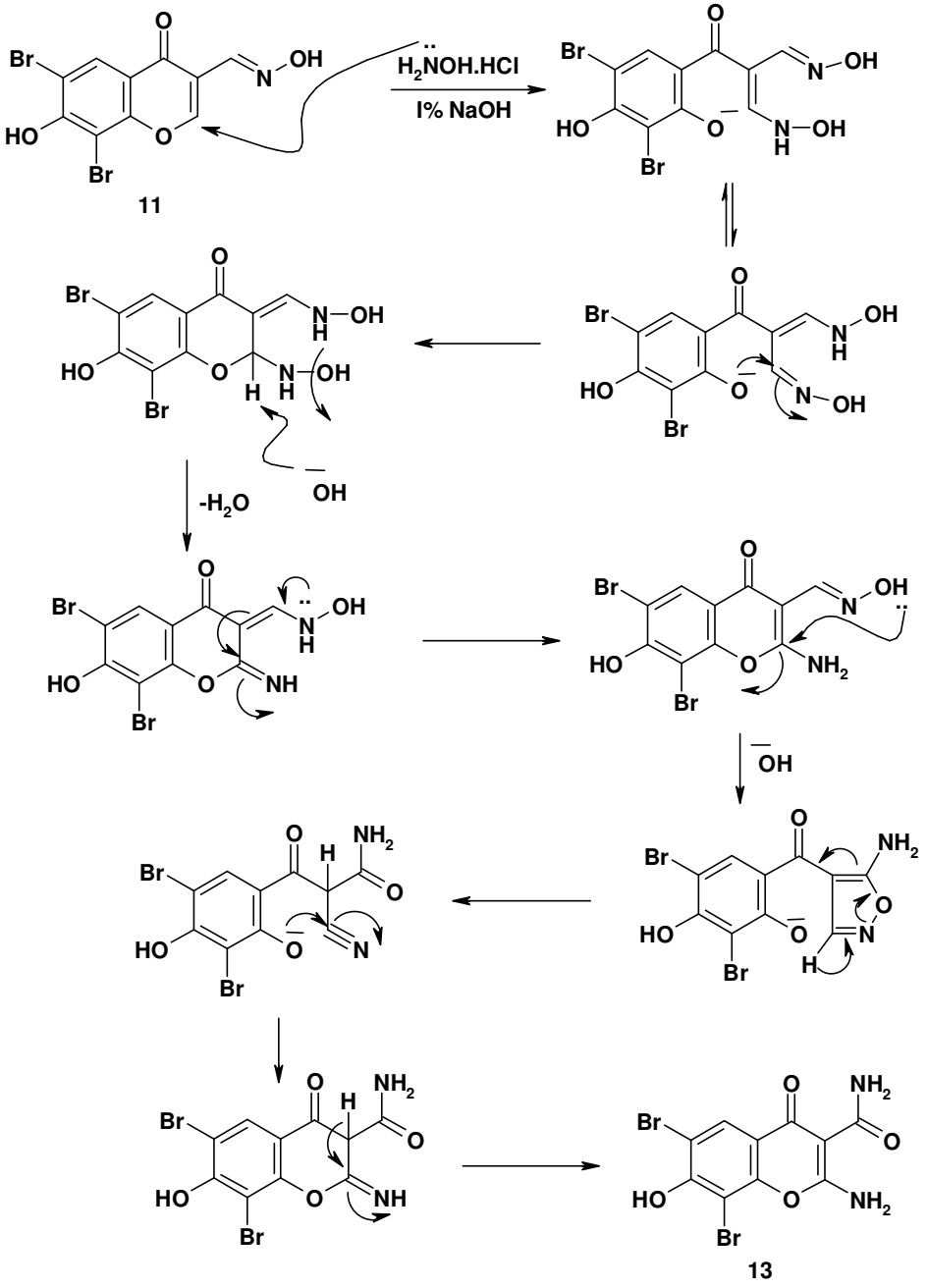
Oxidative cyclization of thiosemicarbazone **6** using $FeCl_3$ in aqueous dioxane afforded 3-(5-amino-1,3,4-thiadiazol-2-yl)-6,8-dibromo-7-hydroxy-4*H*-chromen-4-one (**10**). Compound **10** showed exchangeable signal at δ 7.19 ppm attributed to NH_2 protons, in addition to two singlet signals at δ 8.07 and 8.94 ppm assigned to H-$5_{chromone}$ and H-$2_{chromone}$, respectively (Scheme 2).

The reaction of carboxaldehyde **4** with hydroxylamine hydrochloride was studied under different condensations. Thus, condensation of **4** hydroxylamine hydrochloride in aqueous ethanol afforded the corresponding oxime **11**, while in ethanol containing conc. HCl gave the corresponding carbonitrile **12** [25] (Scheme 4). The IR spectrum of carbonitrile **12** showed characteristic absorption band at 2216 cm^{-1} attributed to C≡N group. Its ^{1}H-NMR spectrum consists of two singlet signals at δ 8.19 and 8.96 ppm due to H-5 and H-2, respectively, in addition to exchangeable signal at δ 12.44 ppm assigned to the OH proton.

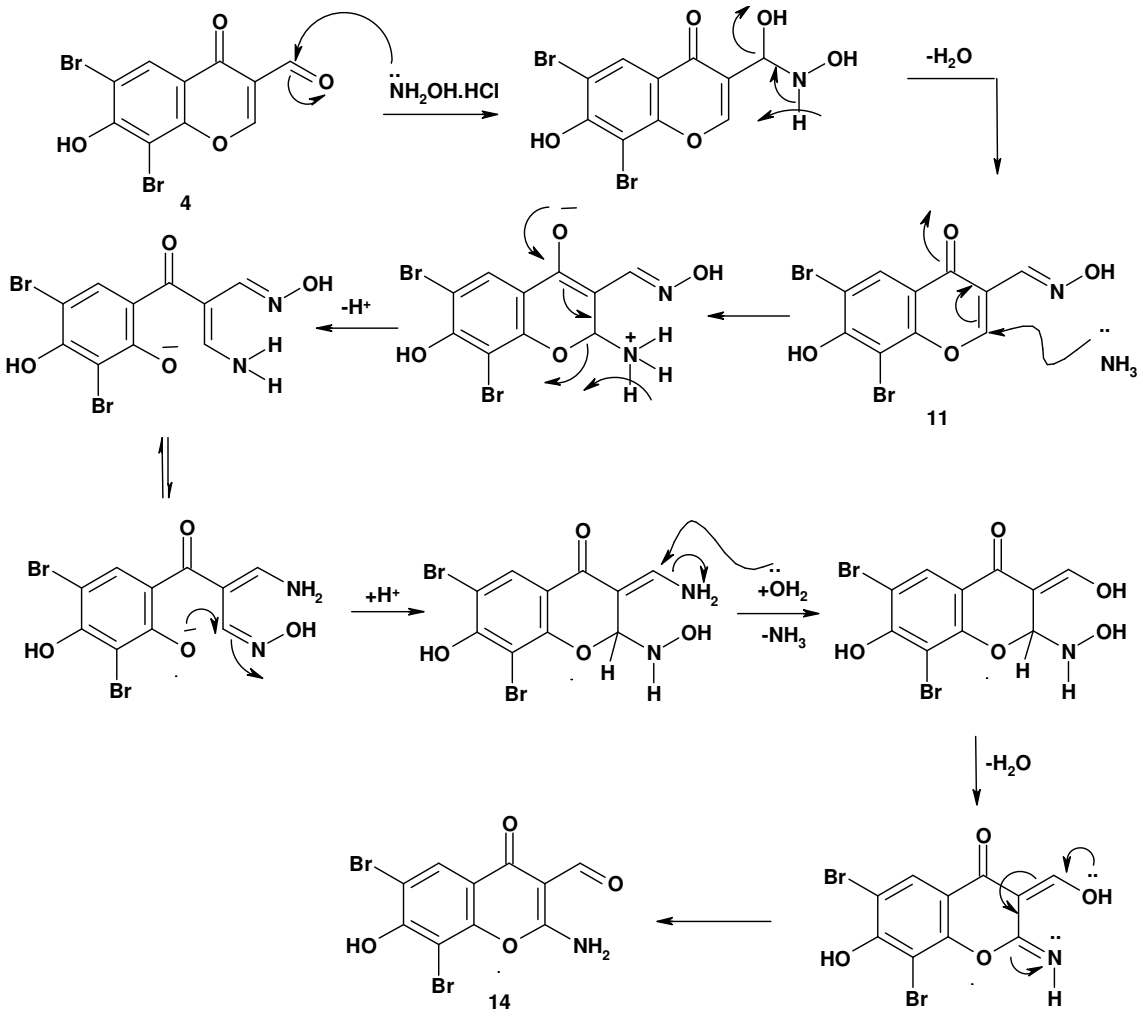


Scheme 4. Chemical behavior of carboxaldehyde **4** with hydroxylamine hydrochloride.

On the other hand, reaction of **4** with $H_2NOH.HCl$ in ethanol containing 1% potassium hydroxide solution gave 2-aminochromone-3-carboxamide derivative **13** [26]. When the latter reaction occurs in ethanol containing ammonium hydroxide, 2-aminochromone-3-carboxaldehyde **14** was obtained [27] (Scheme 4). The proposed mechanism for the formation of carboxamide **13** and carboxaldehyde **14** is depicted Schemes 5 and 6, respectively [28]. Structures of compounds **13** and **14** were deduced from their correct elemental analysis and spectral data. The ^{1}HNMR spectrum of carboxamide **13** showed characteristic singlet due to H-5 at δ 8.05 ppm, in addition to four exchangeable signals due to four NH protons at δ 7.45, 9.31, 9.46 and 10.52 ppm. Carboxamide **13** was further deduced from its mass spectrum which showed the molecular ion peak at m/z 376 which agree well with the molecular formula ($C_{10}H_6Br_2N_2O_4$) and supports the identity of the structure. The mass fragmentation pattern of compound **13** is depicted in Figure 2. On the other hand, the ^{1}HNMR spectrum of carboxaldehyde **14** showed two characteristic singlet signals due to the H-5 and aldehydic proton at δ 8.16 and 10.07 ppm in addition to two exchangeable signals at δ 9.47 and 9.83 ppm attributed to the NH_2 protons.



Scheme 5. The Suggested mechanism for the formation of carboxamide **13**.



Scheme 6. The Suggested mechanism for the formation of carboxaldehyde **14**.

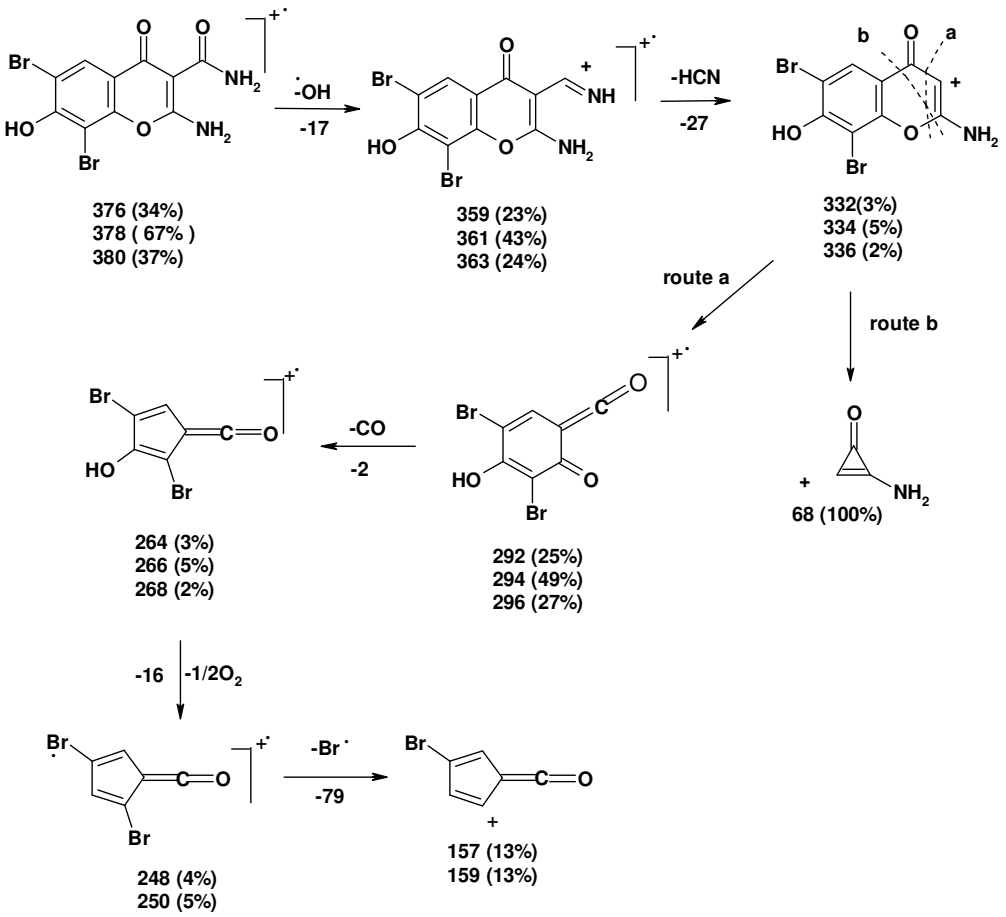


Figure 2. Mass fragmentation pattern of 2-aminochromone-3-carboxamide **13**.

Experimental

Melting points were determined on a digital Stuart SMP3 apparatus. Infrared spectra were measured on Perkin-Elmer 293 spectrophotometer (cm^{-1}), using KBr disks. ^1H NMR (300 MHz) spectra were measured on Mercury-300BB, using DMSO-d_6 as a solvent and TMS (δ) as the internal standard. Mass spectra were obtained using GC-2010 Shimadzu Gas chromatography instrument mass spectrometer (70 eV). Elemental microanalyses were performed on a Perkin-Elmer CHN-2400 analyzer.

3,5-Dibromo-2,4-dihydroxyacetophenone (3)

To a solution of 2,4-dihydroxyacetophenone (**2**) (15.2 g, 0.1 mol) in acetic acid, bromine (16 g, 5.2 mL, 0.1 mol) in acetic acid (10 mL), was added drop wise with continuous stirring for 15 min. The solid obtained was filtered off and crystallized from EtOH/H_2O to give **3** as white crystals, yield (14.4 g, 46%), m.p. 173 ºC (lit. 172-173) [21]. IR (KBr, cm^{-1}): 2964 (br, OH), 1614 ($C=O_{hydrogen\ bonded}$), 1605 (C=C). ^1H-NMR

(DMSO-d_6): 2.33 (s, 3H, CH_3), 7.69 (s, 1H, Ar-H), 8.40 (bs, 1H, OH exchangeable with D_2O), 14.05 (bs, 1H, OH exchangeable with D_2O).

6,8-Dibromo-7-hydroxy-4-oxo-4*H*-chromene-3-carboxaldehyde (4).

Method A: Phosphoryl chloride (3 mL) was added drop wise to a pre-cooled DMF (10 mL) and the mixture was stirred at room temperature for 30 min. Then 3,5-dibromo-2,4-dihydroxyacetophenone (0.93 g, 3 mmol) in DMF (10 mL) was added drop wise with continuous stirring. The mixture was stirred at room temperature for 2h, left overnight and poured onto crushed ice (50 g). The solid obtained was filtered off, air dried and crystallized from ethanol to give compound **4** as yellow crystals, yield (0.8 g, 77%), m.p. 250-251 ^{o}C.

Method B: A mixture of 7-hydroxychromone-3-carboxaldehyde (**5**) (0. 57 g, 3 mmol) and bromine (0.48 g, 0.16 mL, 3 mmol) in acetic acid (80%, 5 mL) was stirred at room temperature for 1 h. The solid obtained was filtered off and crystallized from ethanol to give compound **4** as yellow crystals, yield (0.61 g, 59%), m.p. 250-251 ^{o}C. IR (KBr, cm^{-1}): 3235 (OH), 3058 ($CH_{arom.}$), 1685 ($C=O_{ald.}$), 1667 ($C=O_{\gamma\text{-pyrone}}$), 1599 (C=C). ^{1}H-NMR (DMSO-d_6): 8.16 (s, 1H, H-5), 8.89 (s, 1H, H-2), 10.07 (s, 1H, CH=O). M/z (*I* %) (M/ M+2/ M+4): 346 (M^+, 2)/ 348 (M+2, 5)/ 350 (M+4, 2), 318 (50)/ 320 (100)/ 322 (52), 292 (8)/ 294 (16)/ 296 (8), 276 (3)/ 278 (7)/ 280 (3), 213 (2)/ 215 (2), 197 (3)/ 199 (3), 185 (4)/ 187 (3), 173 (2)/ 175 (2), 157 (2)/ 159 (2), 133 (3), 119 (2), 91 (2). Anal. Calcd for $C_{10}H_4Br_2O_4$ (347.94): C, 34.52; H, 1.16%. Found: C, 33.87; H, 1.16%.

Synthesis of hydrazones 6-8; General procedure

A mixture of carboxaldehyde **4** (0.35 g, 1 mmol) and hydrazine derivatives namely, thiosemicarbazide, N^4-phenylthiosemicarbazide and *S*-benzyl dithiocarbazate (1 mmol) in absolute ethanol (20 mL) was refluxed for 15 min. The solid obtained after cooling was filtered off and crystalline from ethanol to give compounds **6-8**, respectively, as yellow crystals.

2-[(6,8-Dibromo-7-hydroxy-4-oxo-4*H*-chromen-3-yl)methylidene]hydrazine-carbothioamide (6)

Yield (0.31 g, 74%), m.p. 200 ºC. IR (KBr, cm^{-1}): 3437, 3308, 3206 (OH, NH_2, NH), 3031 ($CH_{arom.}$), 1660 ($C=O_{\gamma\text{-pyrone}}$), 1637 (C=N), 1598 (C=C). ^{1}H-NMR (DMSO-d_6):

7.95 (s, 1H, NH exchangeable with D_2O), 8.06 (s, 1H, NH exchangeable with D_2O), 8.16 (s, 1H, CH=N), 8.24 (s, 1H, H-5), 9.19 (s, 1H, H-$2_{chromone}$), 11.54 (s, 1H, NH exchangeable with D_2O). Anal. Calcd for $C_{11}H_7Br_2N_3O_3S$ (421.06): C, 31.38; H, 1.68; N, 9.98; S, 7.62%. Found: C, 31.26; H, 1.66; N, 9.54; S, 7.33%.

2-[(6,8-Dibromo-7-hydroxy-4-oxo-4*H*-chromen-3-yl)methylidene]-*N*-phenylhydrazinecarbothioamide (7)

Yield (0.27 g, 54%), m.p. 197 ºC. IR (KBr, cm^{-1}): 3250, 3126 (OH, 2NH), 1653 (C=$O_{\gamma\text{-pyrone}}$), 1602 (C=N), 1541 (C=C), 1300 (C=S). ^{1}H-NMR (DMSO-d_6): 6.92-7.01 (m, 2H, Ar-H), 7.34-7.53 (m, 3H, Ar-H), 8.35 (s, 1H, CH=N), 8.41 (s, 1H, H-5), 8.99 (s, 1H, H-$2_{chromone}$), 10.40 (bs, 1H, NH), 11.59 (bs, 1H, NH), 13.15 (bs, 1H, OH). Anal. Calcd for $C_{17}H_{11}Br_2N_3O_3S$ (497.16): C, 41.07; H, 2.23; N, 8.45; S, 6.45%. Found: C, 41.11; H, 2.21; N, 8.39; S, 6.27%.

Benzyl 2-[(6,8-dibromo-7-hydroxy-4-oxo-4*H*-chromen-3-yl)methylidene]hydrazine carbodithioate (8)

Yield (0.34 g, 64%), m.p. 220 ºC. IR (KBr, cm^{-1}): 3355 (OH), 3180 (NH), 3015 ($CH_{arom.}$), 2984 ($CH_{aliph.}$), 1634 (C=$O_{\gamma\text{-pyrone}}$), 1610 (C=N), 1588 (C=C), 1286 (C=S). ^{1}H-NMR (DMSO-d_6): 4.57 (s, 2H, CH_2), 6.92-6.95 (m, 2H, Ar-H), 7.30-7.33 (m, 3H, Ar-H), 8.29 (s, 1H, H-5), 8.58 (s, 1H, CH=N), 9.38 (s, 1H, H-2), 10.20 (bs, 1H, NH exchangeable with D_2O).Anal. Calcd for $C_{18}H_{12}Br_2N_2O_3S_2$ (528.24): C, 40.93; H, 2.29; N, 5.30; S, 12.14%. Found: C, 40.87; H, 2.30; N, 5.13; S, 11.94%.

(3,5-Dibromo-2,4-dihydroxybenzoyl)-1*H*-pyrazole (9)

Method A: A mixture of carboxaldehyde **4** (0.35 g, 1 mmol) and hydrazine derivatives namely, thiosemicarbazide, N^4-phenylthiosemicarbazide and *S*-benzyl dithiocarbazate (1 mmol) in DMF (10 mL) was refluxed for 30 min. The solid obtained after cooling was filtered off and crystalline from methanol to give compound **9** as yellow crystals, yield (55-61%), m.p. 262 ^{o}C.

Method B: A mixture of carboxaldehyde **4** (0.70 g, 2 mmol) and hydrazine hydrate (0.1 mL, 2 mmol) in absolute ethanol (10 mL) was refluxed for 30 min. The solid obtained after cooling was filtered off and crystalline from methanol to give compound **9** as yellow crystals, yield (0.47 g, 65%), m.p. 262 ^{o}C. IR (KBr, cm^{-1}): 3588, 3265 (2OH, NH), 1635 (C=O), 1617 (C=N), 1603 (C=C). ^{1}H-NMR (DMSO-d_6): 7.84 (s, 1H,

H-5$_{resorcinol}$), 8.32 (s, 1H, H-5$_{pyrazole}$), 8.59 (s, 1H, H-5$_{pyrazole}$), 10.34 (bs, 1H, NH exchangeable with D_2O), 10.80 (bs, 1H, OH exchangeable with D_2O). M/z (*I* %) (M/ M+2/ M+4): 360 (M^+, 9)/ 362 (M+2, 18)/ 364 (M +4, 10), 343 (46)/345 (81)/ 347 (46), 292 (6)/ 294 (9)/ 296 (6), 185 (8)/ 187 (8), 157 (9)/ 159 (10), 129 (18), 118 (14), 95 (30), 80 (100), 77 (57), 64 (27). Anal. Calcd for $C_{10}H_6Br_2N_2O_3$ (361.97): C, 33.18; H, 1.67; N, 7.74%. Found: C, 33.15; H, 1.64; N, 7.76%.

3-(5-Amino-1,3,4-thiadiazol-2-yl)-6,8-dibromo-7-hydroxy-4*H*-chromen-4-one (10).

A mixture of thiosemicarbazone **4** (0.42 g, 1 mmol) and ferric chloride (2 mmol) in aqueous dioxane (80%, 30 mL) was refluxed for 2 h. The solid obtained during heating was filtered off and stirred with 10% aqueous sodium carbonate solution for 2 h, the reaction mixture was filtered off, and the product was crystalline from DMF to give compound **10** as yellow crystals, yield (0.31 g, 74%), m.p. > 300 ^oC. IR (KBr, cm^{-1}): 3440, 3347 (OH, NH_2), 3083 ($CH_{arom.}$), 1623 (C=O), 1612 (C=N), 1553 (C=C). ^{1}H-NMR (DMSO-d_6): 7.19 (bs, 2H, NH_2 exchangeable with D_2O), 8.07 (s, 1H, H-5$_{chromone}$), 8.94 (s, 1H, H-2$_{chromone}$). Anal. Calcd for $C_{11}H_5Br_2N_3O_3S$ (419.05): C, 31.53; H, 1.20; N, 10.03; S, 7.65%. Found: C, 31.36; H, 1.18; N, 9.87; S, 7.36%.

6,8-Dibromo-7-hydroxy-4-oxo-4*H*-chromene-3-carboxaldehyde-oxime (11).

To a solution of carboxaldehyde **4** (0.70 g, 2 mmol) in 95% ethanol (15 mL), hydroxylamine hydrochloride (0.15 g, 2.2 mmol) in water (10 mL) was added. The reaction mixture was refluxed for 10 min. The solid obtained after cooling was filtered off and crystallized from DMF/H_2O to give compound **11** as yellow crystals, yield (0.51 g, 70%), m.p > 300 °C. IR (KBr, cm^{-1}): 3274 (2 OH), 1660 (C=O $_{\gamma\text{-pyrone.}}$), 1620 (C=N), 1590 (C=C). Anal. Calcd for $C_{10}H_5Br_2NO_4$ (362.96): C, 33.09; H, 1.39; N, 3.86%. Found: C, 32.78; H, 1.31; N, 3.59%.

6,8-Dibromo-7-hydroxy-4-oxo-4*H*-chromene-3-carbonitrile (12).

A mixture of carboxaldehyde **4** (0.70 g, 2 mmol) and hydroxylamine hydrochloride (0.15 g, 2.2 mmol) in 95% ethanol (20 mL) and concentrated HCl (5 mL) was refluxed for 4h. After cooling, the reaction mixture was poured onto crushed ice. The precipitated solid was filtered off and crystallized from ethanol to give compound **12** as pale yellow crystals, yield (0.45 g, 65%), m.p. 275 °C. IR (KBr, cm^{-1}): 3308 (OH), 3020 ($CH_{arom.}$), 2216 (C≡N), 1618 (C=O), 1540 (C=C). ^{1}H-NMR (DMSO-d_6): 8.19 (s, 1H,

H-5), 8.96 (s, 1H, H-2), 12.44 (bs, 1H, OH exchangeable with D_2O). Anal. Calcd for $C_{10}H_3Br_2NO_3$ (344.94): C, 34.82; H, 0.88; N, 4.06%. Found: C, 34.65; H, 0.85; N, 4.02%.

2-Amino-6,8-dibromo-7-hydroxy-4-oxo-4*H*-chromene-3-carboxamide (13).

A mixture of carboxaldehyde **4** (0.70 g, 2 mmol) and hydroxylamine hydrochloride (0.15 g, 2.2 mmol) in ethanol (10 mL) and NaOH solution (1%, 10 mL), was heating on a water bath for 2h. After cooling, the reaction mixture was neutralized with HCl. The solid deposited was filtered off and crystallized from acetic acid to give compound **13** as yellow crystals, yield (0.36 g, 48%), m.p . 300 °C. IR (KBr, cm^{-1}): 3446, 3308, 3253, 3142 (OH, 2 NH_2), 1640 (2 C=O), 1593 (C=C). ^{1}H-NMR (DMSO-d_6): 7.45 (bs, 1H, NH exchangeable with D_2O), 8.05 (s, 1H, H-5), 9.31(bs, 1H, NH exchangeable with D_2O), 9.46 (bs, 1H, NH exchangeable with D_2O), 10.52 (bs, 1H, NH exchangeable with D_2O). M/z (*I* %) (M/ M+2/ M+4): 376 (M^+, 34)/ 378 (M+2, 67)/ 380 (M +4, 34), 359 (23)/361 (43)/ 363 (24), 332 (3)/ 334 (5)/ 336 (2), 292 (25)/ 294 (49)/ 296 (24), 264 (3)/ 266 (5)/ 268 (2), 248 (4)/ 250 (5), 157 (13)/ 159 (13), 77 (38), 68 (100). Anal. Calcd for $C_{10}H_6Br_2N_2O_4$ (377.97): C, 31.78; H, 1.60; N, 7.41%. Found: C, 31.66; H, 1.52; N, 7.19%.

2-Amino-6,8-dibromo-7-hydroxy-4-oxo-4*H*-chromene-3-carboxaldehyde (14).

A mixture of carboxaldehyde **4** (0.70 g, 2 mmol) and hydroxylamine hydrochloride (0.15 g, 2.2 mmol) in 95% ethanol (15 mL) was refluxed for 5 min., then ammonium hydroxide (5 mL) was added and the reaction mixture was heated for 30 min. The solid obtained during heating was filtered off and crystallized from acetic acid to give compound **14** as yellow crystals, yield (0.43 g, 59%), m.p. > 300 °C. IR: (KBr, cm^{-1}): 3214 (OH, NH_2), 3072 ($CH_{arom.}$), 1675 ($C=O_{ald.}$), 1656 ($C=O_{\gamma\text{-pyrone}}$), 1594 (C=C). ^{1}H-NMR (DMSO-d_6): 8.16 (s, 1H, H-5), 8.89 (s, 1H, H-2), 9.47 (s, 1H, NH exchangeable with D_2O), 9.83 (s, 1H, NH exchangeable with D_2O), 10.07 (s, 1H, CH=O). Anal. Calcd for $C_{10}H_5Br_2NO_4$ (362.96): C, 33.09; H, 1.39; N, 3.86%. Found: C, 32.82; H, 1.28; N, 3.69%.

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