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A New Pathway to 3-Hetaryl-2-oxo-2*H*-chromenes: On the Proposed Mechanisms for the Reaction of 3-Carbamoyl-2-iminochromenes with Dinucleophiles

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Abstract: The present account summarizes the author's studies to elucidate the mechanisms of the recently reported rearrangements resulting from *inter*- and/or *intra*molecular reactions of 2-imino-2*H*-chromene-3-carboxamides with different dinucleophiles.

Keywords: rearrangements, mechanisms, iminochromenes, nucleophiles.

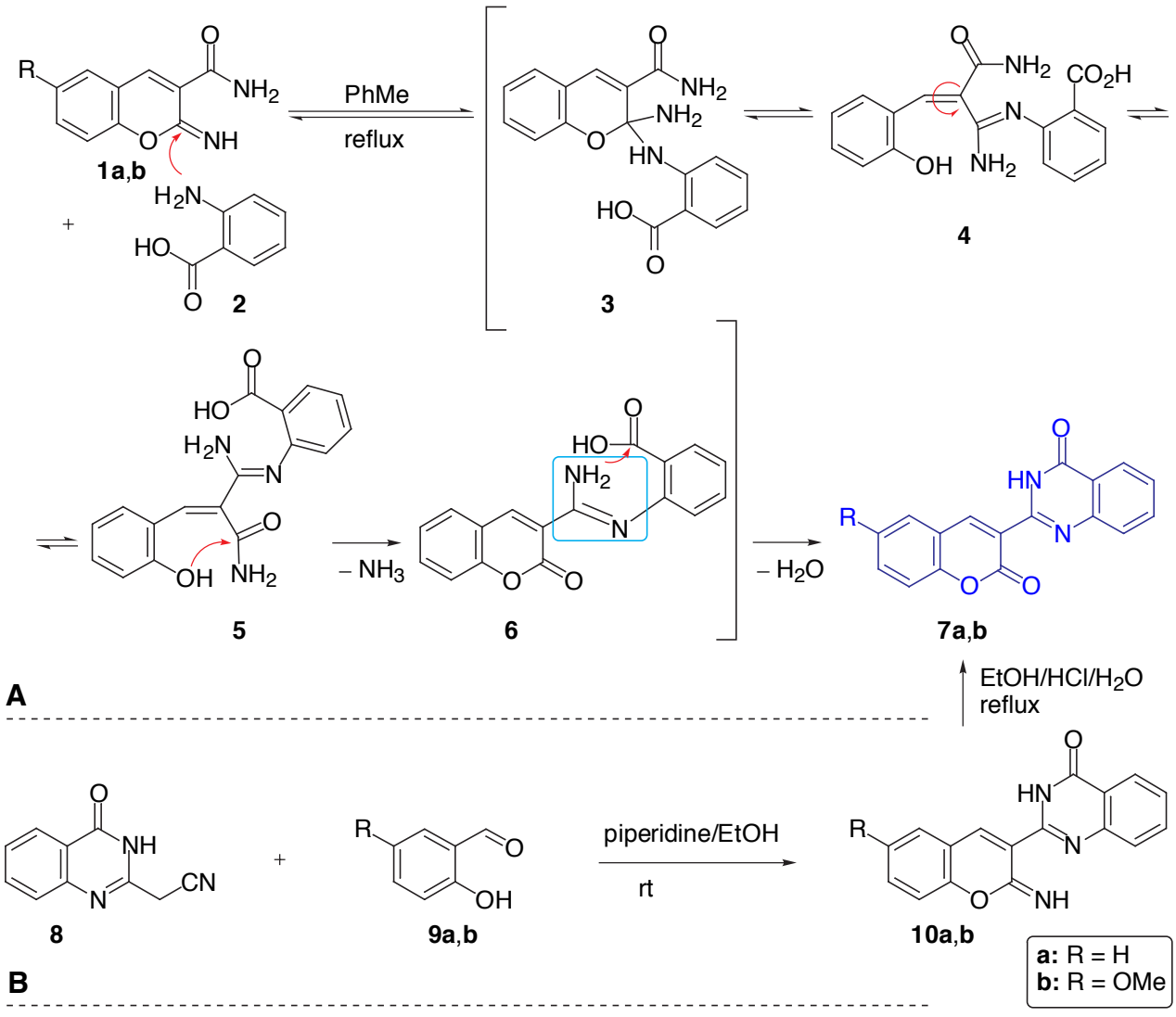
Introduction

The coumarin (2*H*-chromen-2-one) moiety is often found in natural products [1]. In view of the ubiquity of this fragment in a variety of biologically active compounds, the synthesis of various 2*H*-chromen-2-one analogs is important in gauging their potential as a source of chemotherapeutics [2]. As part of our investigations on the reactivity of 3-carbamoyl-2-imino-2*H*-chromenes [3], we recently introduced a new method for synthesis of 3-hetaryl-2-oxo-2*H*-chromenes [4]. This method was based on the rearrangements of 2-imino-2*H*-chromene-3-carboxamides into 3-hetaryl-2-oxo-2*H*-chromenes under the action of dinucleophiles. In this account, results of our studies on clarification of the mechanism of the above-mentioned rearrangements are summarized and exemplified by utilizing anthranilic acid, its derivatives, and arylhydrazides as *N*-nucleophiles. In order to elucidate the

mechanisms of the applied rearrangements, a model system approach based on isolation of stable reaction intermediates or their structural analogs was used.

Results and Discussion

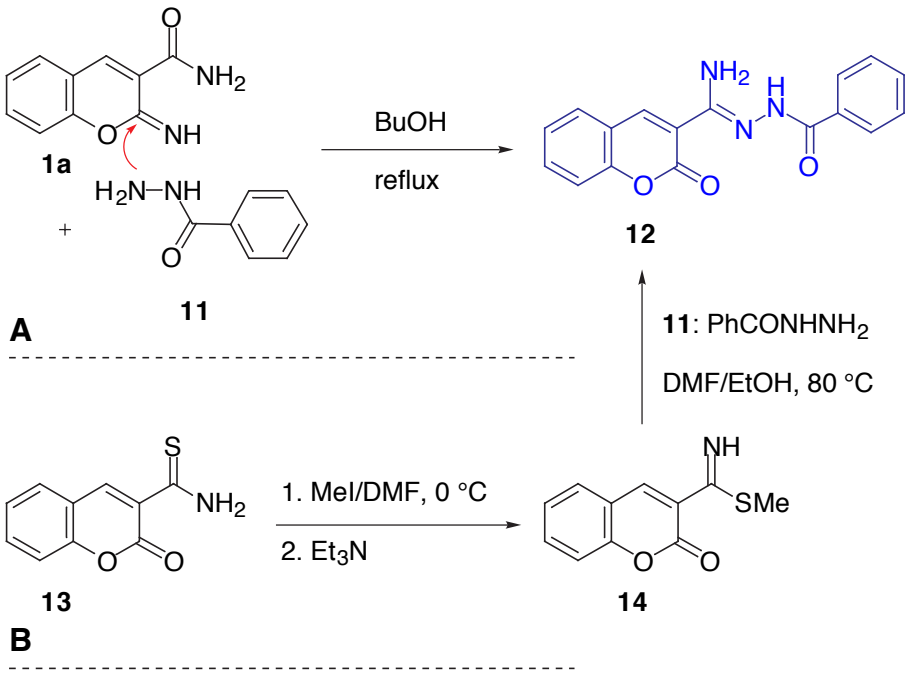
Several methods for synthesis of quinazolinylcoumarin derivatives of type **7** have been reported. For example, compounds of type **7** have been prepared by aminolysis of 4-oxo-2-(2-oxo-2*H*-chromen-3-yl)-4*H*-3,1-benzoxazines with aqueous ammonia [5], ammonium acetate or formamide [6]. Various



Scheme 1. Proposed mechanism for the transformations of 2-imino-2*H*-chromenes **1** into 3-(quinazolin-2-yl)-2*H*-chromen-2-ones **7** by the action of anthranilic acid (**2**) under non-acidic conditions

7-diethylamino-3-(4-oxo-3*H*-quinazolin-2-yl)-2*H*-chromen-2-one dyes have been synthesized [7] by the reactions of: (i) ethyl 7-diethylamino-2-oxo-2*H*-chromene-3-carboxylate with anthranilamides; (ii) cyclization of 4-diethylamino-2-hydroxybenzaldehyde with 2-(cyanomethyl)quinazolin-4(3*H*)-ones; (iii) 7-amino-2-oxo-2*H*-chromene-3-carboxamides with isatoic anhydride or of 4-diethylamino-2-hydroxybenzaldehyde with acetanilides and subsequent cyclization of the product formed with urethane and phosphorus pentoxide.

Kametani *et al*. reported [8] the synthesis of 3-substituted quinazolin-4(3*H*)-ones starting from a sulfinamide anhydride, prepared from anthranilic acid (**2**) and thionyl chloride, and primary and secondary amides. Our attempts to synthesize quinazolinylcoumarin **7a** by simple heating of 2-oxo-2*H*-chromene-3-carboxamide (**25** [9], *cf*. Scheme 9) and anthranilic acid (**2**) without any additional reagents failed. However, it was found that refluxing of compounds **1a**,**b** and **2** in degassed toluene afforded compounds **7a**,**b** in moderate yields as the sole products (Scheme 1A). In the course of the reaction, a strong liberation of ammonia was detected. In order to fully characterize compounds **7a**,**b**, they were also synthesized by an alternative method *via* Knoevenagel condensation of 2-(cyanomethyl)quinazolin-4(3*H*)-one **8** [10] with salicylaldehydes **9a**,**b** in ethanol and using piperidine as a catalyst and subsequent acid hydrolysis of the formed imines **10** (Scheme 1B).

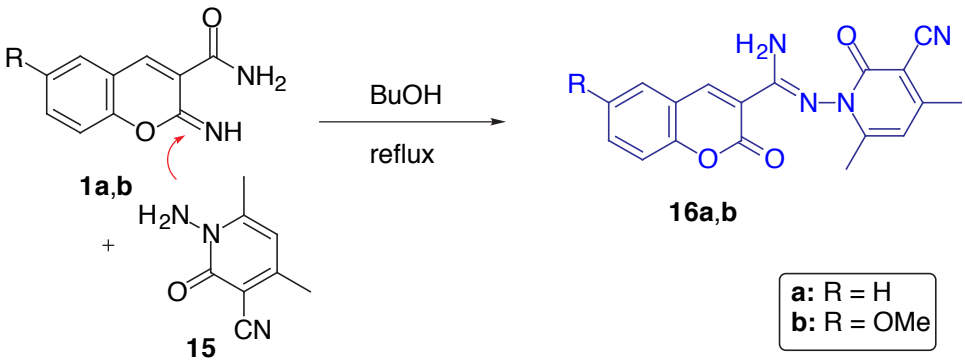


Scheme 2. Synthesis of amide-hydrazone **12** under non-acidic conditions

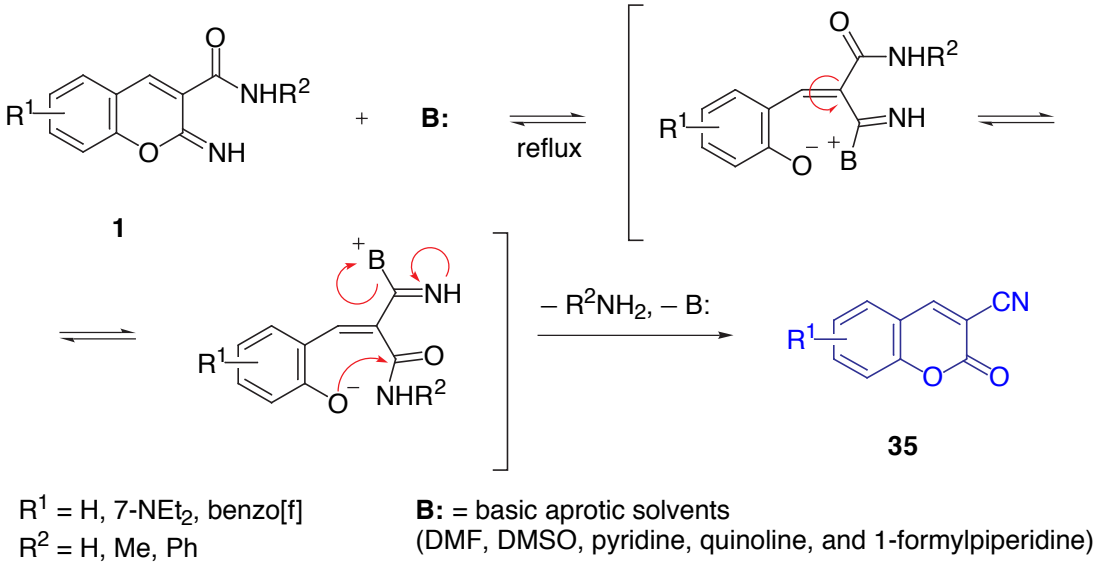
A mechanism was postulated (Scheme 1A) for the formation of 2*H*-chromen-2-one and quinazolin-4(3*H*)-one moieties *via* a rearrangement of 2-imino-2*H*-chromene-3-carboxamides **1** by the action of anthranilic acid (**2**) as *N*-nucleophile [11] under non-acidic conditions. It may involve several consecutive or concerted steps: (i) intermolecular nucleophilic attack of NH_2 on C-2 of the

iminolactone ring (**1** + **2** ⇆ **3**), (ii) iminolactone ring opening (**3** ⇆ **4**), (iii) thermal *E*/*Z* isomerization [12] of intermediate **4** (**4** ⇆ **5**), iv) cyclization of intermediate **5** to amidine **6**; and (v) subsequent formation of 2*H*-chromen-2-one and pyrimidine fragments (**6** → **7**).

To prove the proposed mechanism, we directed our studies to isolation of intermediate amidines of type **6**. With this objective in view various heterocyclic systems, not prone to spontaneous cyclization, were designed and synthesized. As an example, refluxing of iminocarboxamide **1a** and benzohydrazide (**11**) (Scheme 2A) in butan-1-ol afforded amide-hydrazone **12**, which was also synthesized independently (Scheme 2B) from chromenethiocarboxamide **13** [13] through the intermediacy of carboximidothioate **14**. Furthermore, amidines **16a**,**b** were synthesized (Scheme 3) in moderate yields employing the same rearrangement conditions.



Scheme 3. Synthesis of amidines **16** under non-acidic conditions



Scheme 4. Proposed mechanism for the transformations of substituted 2-imino-2*H*-chromenes **1** in basic aprotic solvents

It was also shown that 2-imino-2*H*-chromene-3-carboxamides of type **1** undergo transformation into 2-oxo-2*H*-chromene-3-carbonitriles **35** in basic aprotic solvents: DMF, DMSO, pyridine, quinoline and *N*-formylpiperidine (Scheme 4) [14]. In contrast, the corresponding 2-oxo-2*H*-chromene-3-carboxamides **1** did not undergo dehydration to afford 2-oxo-2*H*-chromene-3-carbonitriles even after prolonged boiling for 3–4 h in the above-mentioned solvents. The reaction mechanism of this transformation should be analogous to that presented in Scheme 1A. In this case, solvent acts as a nucleophile and opens the iminolactone ring (**1** + base) and then is eliminated with the formation of nitrile group (**1** → **35**, Scheme 4).

In connection with this, a study on isomerization of chromen-2-imines in DMSO-d_6 has to be mentioned. O'Callaghan *et al*. revealed [15] that when unsubstituted 2-imino-2*H*-chromene-3-carboxamide (**1a**) was dissolved in DMSO-d_6, the NMR spectra showed that a mixture of both 2-imino-2*H*-chromene-3-carboxamide and the isomeric 2-cyano-3-(2-hydroxyphenyl)-prop-2-enamide (Figure 1) was present. Other chromen-2-imines behaved similarly, but the degree of isomerization varied considerably, depending on the nature and position of the substituents.

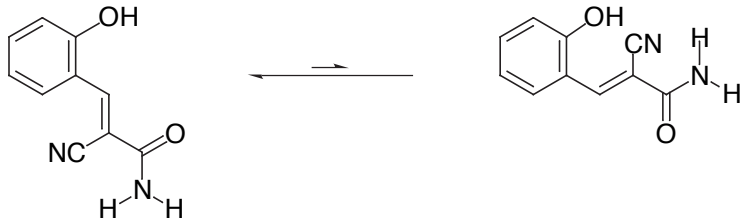
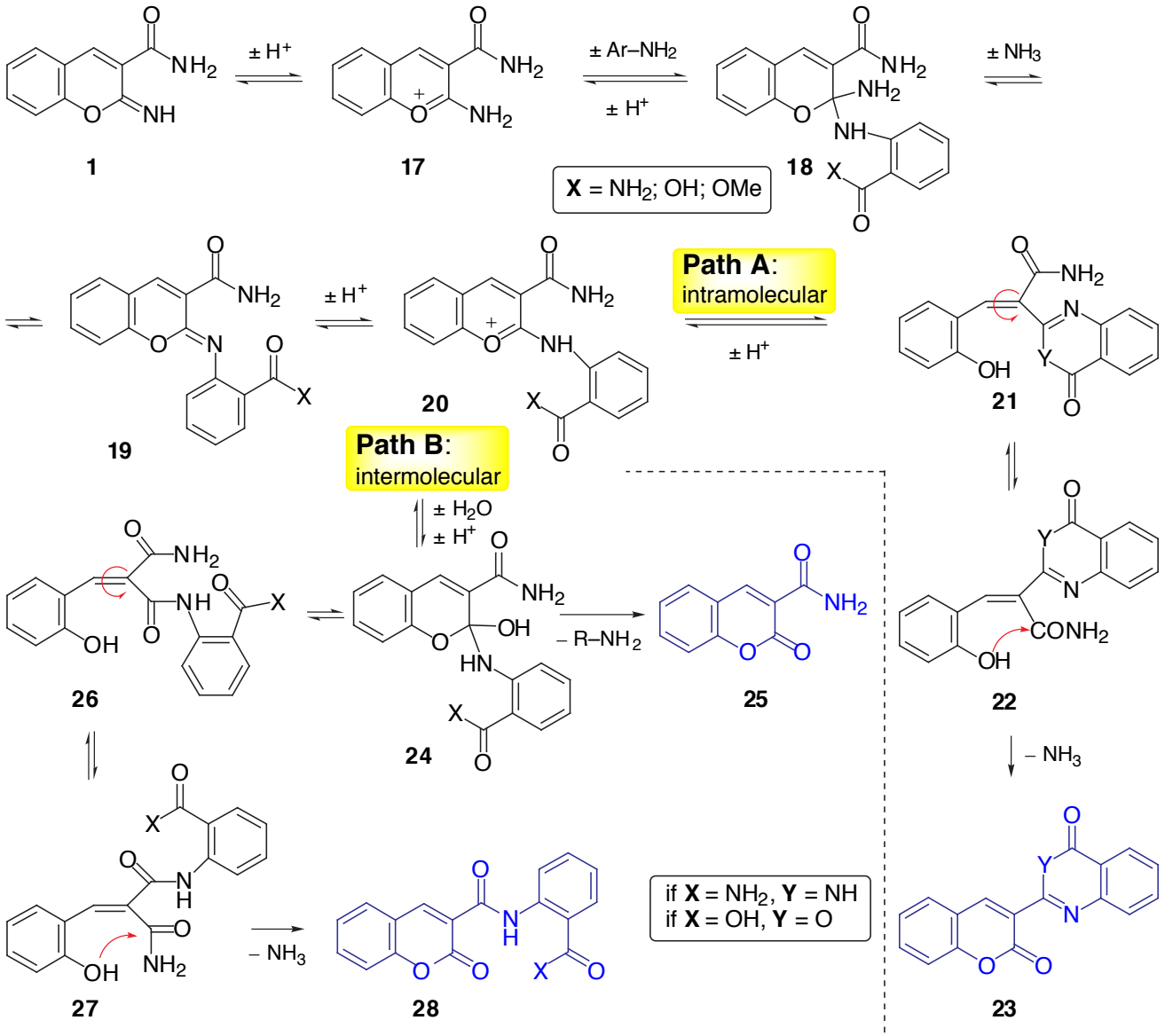


Figure 1.

As shown in Scheme 5 (paths A and B), two distinct pathways leading to different products were envisioned to be involved in the *acid-catalyzed* rearrangements of 2-imino-2*H*-chromene-3-carboxamides **1**. Thus, depending on reaction conditions, two types of products might be formed: (i) under non-aqueous acidic conditions compounds, comprising 2*H*-chromen-2-one and quinazoline or benzoxazine moieties **23** (**1** → **19** → **23**, Scheme 5, path A) or (ii) in aqueous acidic media, where H_2O acts as *O*-nucleophile, *N*-substituted 2-oxo-2*H*-chromene-3-carboxamides **28** (**1** → **19** → **28**, Scheme 5, path B). In this case, a competing reaction could be a simple hydrolysis (**19** → **25**), although a full understanding of the factors controlling this competition has not been attained. General intermediates for transformations presented in Scheme 5 are 2-(arylimino)-2*H*-chromenes of type **19**. To verify our assumption of two possible mechanisms of reaction between 2-imino-2*H*-chromene-3-carboxamides **1** and anthranilates in acidic media, we directed our studies to isolation of intermediate 2-(arylimino)-2*H*-chromenes **19** and, starting from them, to the synthesis of 3-substituted 2*H*-chromen-2-ones of type **23** and **28**.

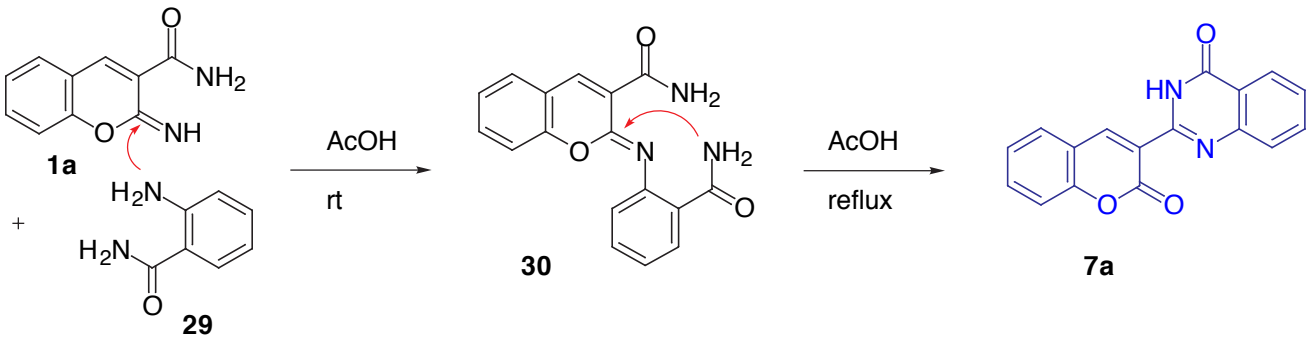
A method for synthesis of 2-(arylimino)chromenes **19** was recently introduced in our laboratory and it was shown that a variety of 2-(aryl- or alkylimino)-substituted 2*H*-chromen-2-ones of type **19** could be prepared [3]. This method is based on aminolysis of cyclic imido esters and is similar to the

reaction of simple imidates with amines [16]. This type of reactions should also be similar to the acid hydrolysis of 2-imino-2*H*-chromenes to 2*H*-chromen-2-ones which proceeds through the formation of the corresponding benzopyrylium salts [17,18].



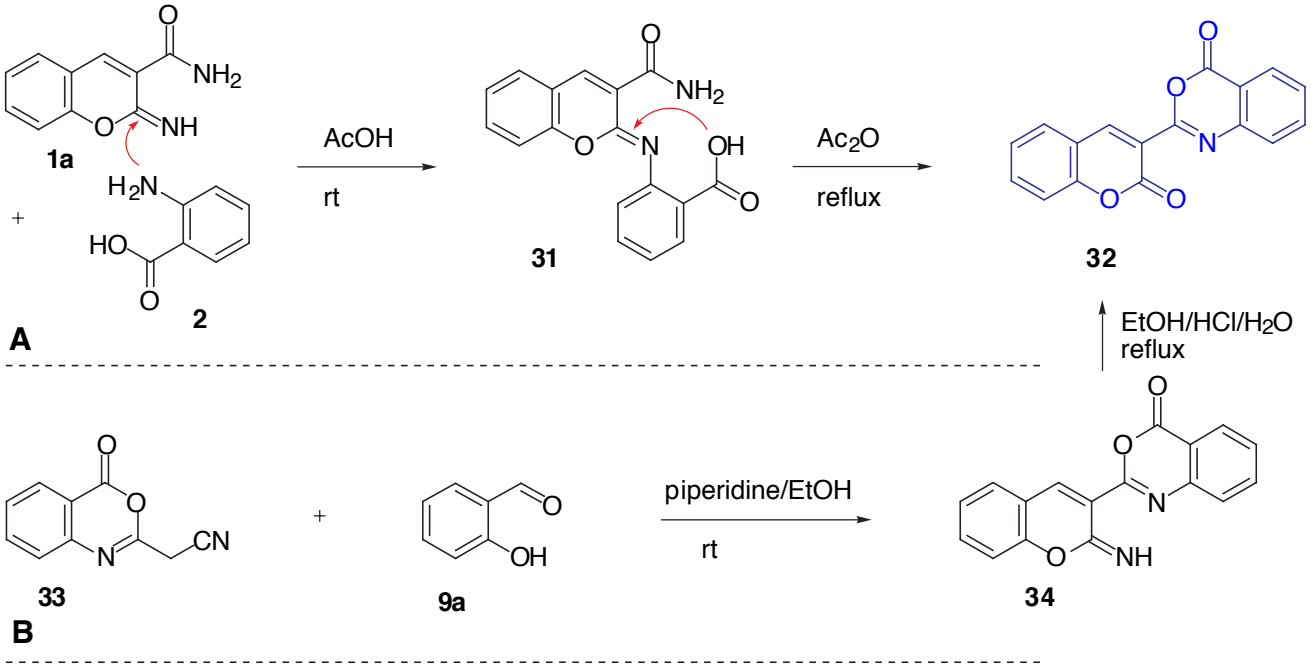
Scheme 5. Proposed mechanism for the transformations of 2-imino-2*H*-chromenes **1** by the action of nucleophiles under acidic conditions

The principal feature of the method for synthesis of 2-(arylimino)chromenes **19** is the use of either amine hydrochloride [3,19,20] or benzopyrylium salts of type **17** [3]. Finally, we found a different methodology [4] based on using glacial acetic acid for *in situ* formation of the corresponding salts, their reaction and subsequent removal of the ammonia released.



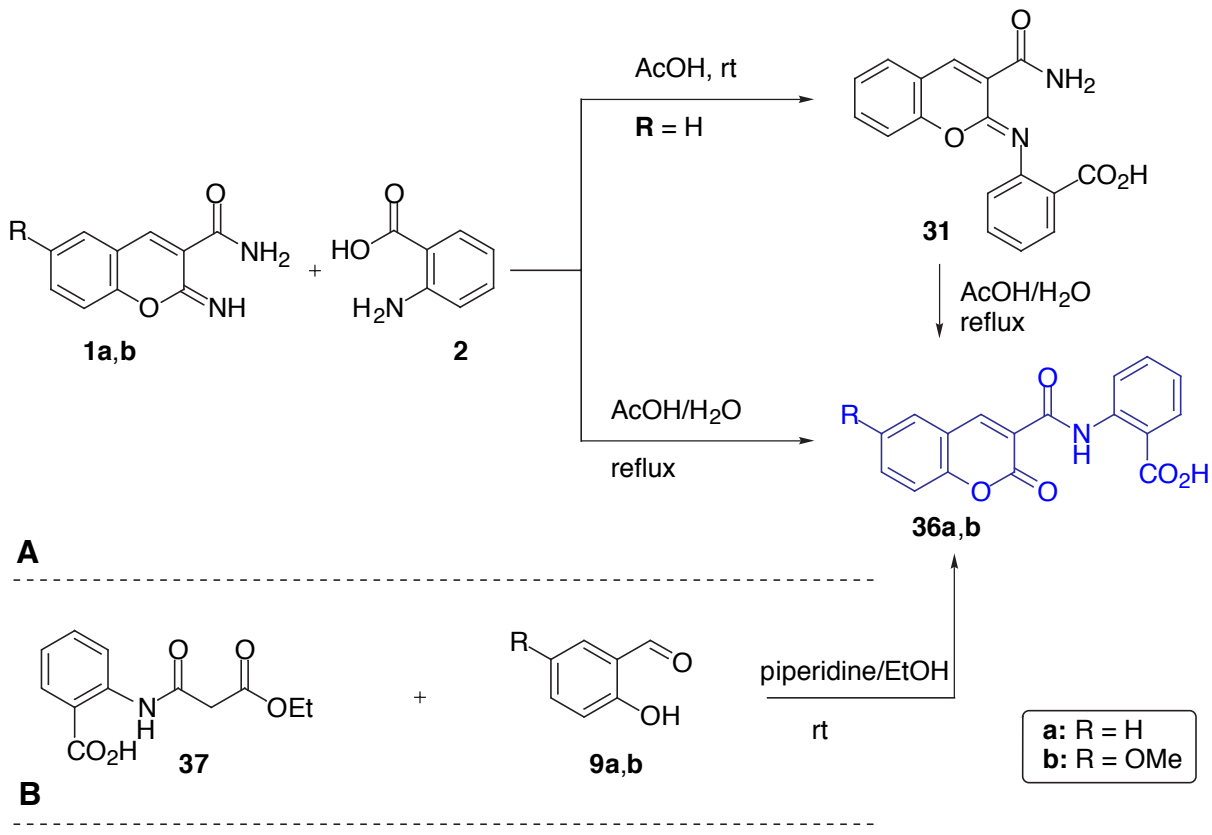
Scheme 6. Synthesis and rearrangement of 2-(arylimino)chromene **30** into 3-(quinazolin-2-yl)-2*H*-chromen-2-one (**7a**) under acidic anhydrous conditions

As shown in Schemes 6–10, syntheses of the desired 2-(arylimino)chromenes **30**, **31**, **39** and **41** were finally performed by adding equivalent amounts of the corresponding 2-iminochromene derivatives **1** to a solution of anthranilates **29**, **2**, **38** or benzohydrazide (**11**) in glacial acetic acid. After stirring the reaction mixture at room temperature, products were precipitated and subsequently isolated, purified, characterized and used for further transformations.



Scheme 7. Synthesis and rearrangement of 2-(arylimino)chromene **31** into 2-(2-oxo-2*H*-chromen-3-yl)-4*H*-3,1-benzoxazin-4-one (**32**) under acidic anhydrous conditions

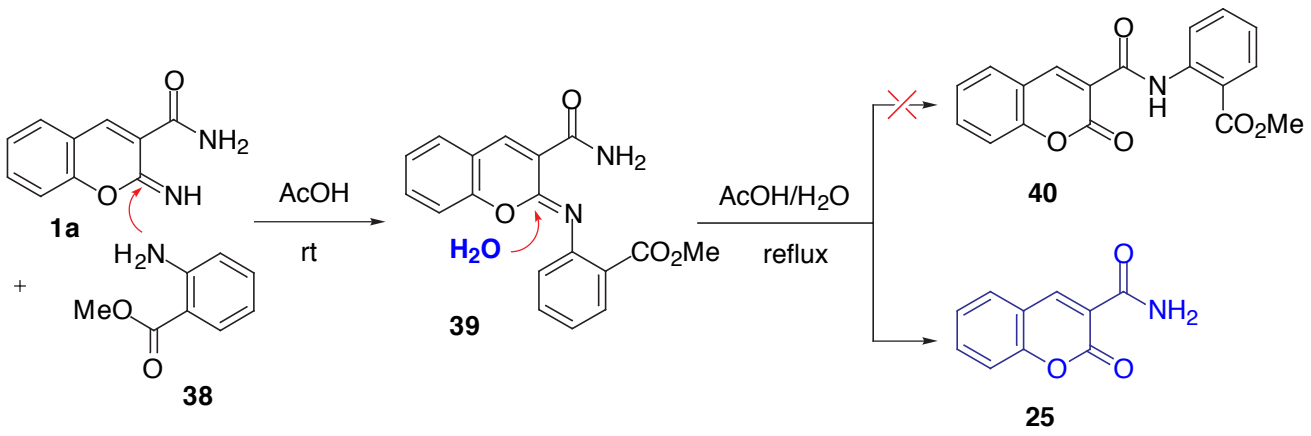
It was found that in acidic anhydrous media (glacial acetic acid or acetic anhydride), 2-(*N*-substituted imino)chromenes **30** and **31** reacted *intra*molecularly (*cf*. Scheme 5, path A) to produce expected derivatives **7a** (Scheme 6) and **32** (Scheme 7A) in good yields.



Scheme 8. Synthesis of *N*-aryl-2-oxo-2*H*-chromene-3-carboxamides **36** in aqueous acidic media

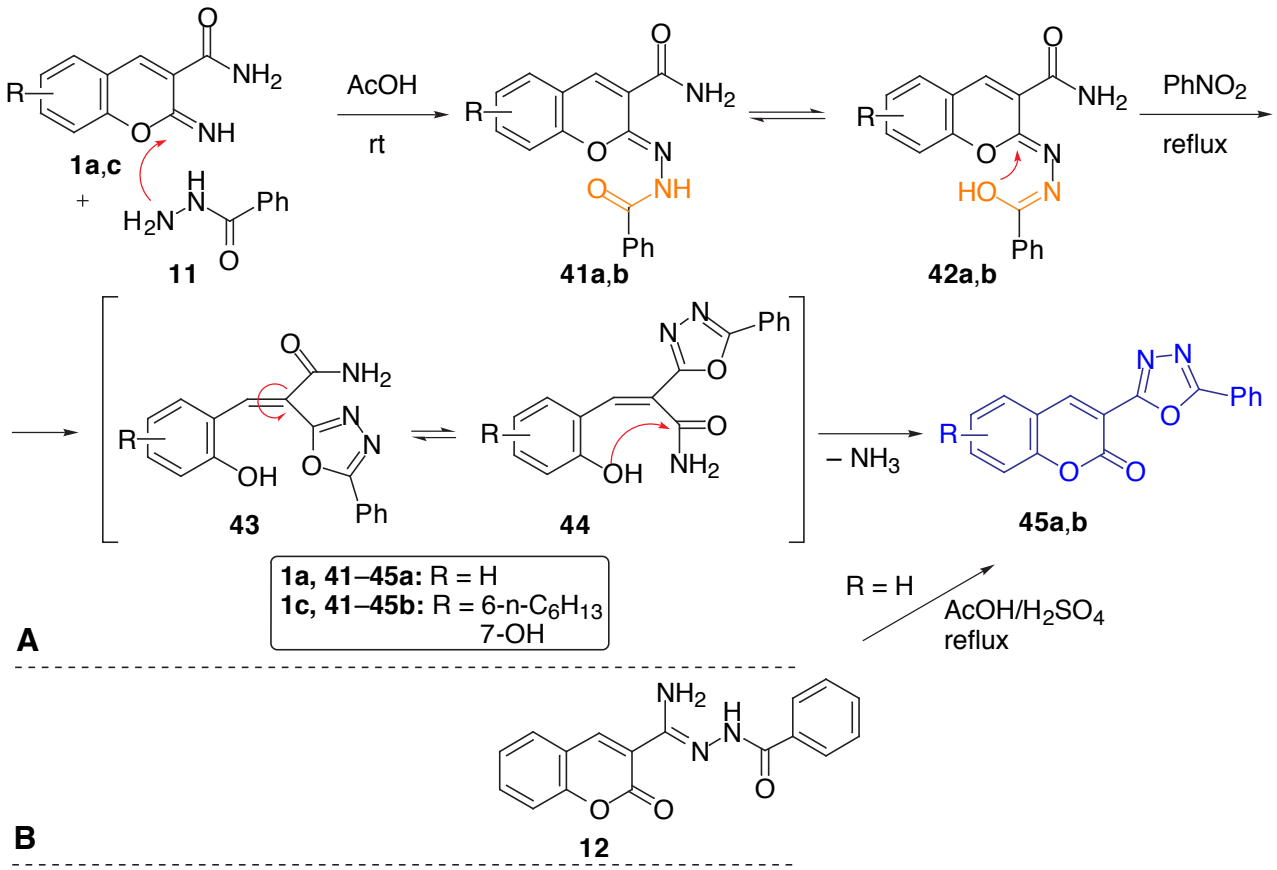
The reaction between imines **1a**,**b** and **2** in aqueous acidic media (80% acetic acid) (Scheme 8A) proceeded differently. Refluxing in this solvent for 2 h gave *N*-(2-carboxyphenyl)-2-oxo-2*H*-chromene-3-carboxamides **36a**,**b**. A mechanism that accounts for the products is detailed in Scheme 5, path B. To prove that mechanism, a reaction between **1a** and **2** (Scheme 8A) was initially performed in acetic acid at room temperature. It took place without iminolactone ring opening and furnished expected intermediate **31**, which was converted into compound **36a** by further boiling in aqueous acetic acid. For unambiguous structure elucidation, 2-(2-oxo-2*H*-chromen-3-yl)-4*H*-3,1-benzoxazin-4-one **32** [21] and *N*-aryl-2-oxo-2*H*-chromene-3-carboxamides **36a**,**b** were also prepared independently from 2-(cyanomethyl)-4*H*-3,1-benzoxazin-4-one **33** [22] or ethyl 2'-carboxymalonanilate **37** [23] and salicylaldehydes **9** as depicted in Schemes 7B and 8B.

Taking into consideration the results observed for synthesis of *N*-aryl-2-oxo-2*H*-chromene-3-carboxamides **36** (Scheme 8A), we examined the possibility of rearrangement of 2-(arylimino)-2*H*-chromene-3-carboxamide **39** into *N*-aryl-2-oxo-2*H*-chromene-3-carboxamide **40** by the action of water as *O*-nucleophile (Scheme 9). However, compound **40** was not detected presumably due to simple hydrolysis (*cf*. Scheme 5, path B), which took place to furnish the known 2-oxo-2*H*-chromene-3-carboxamide **25** [9].



Scheme 9. Attempted synthesis of *N*-aryl-2-oxo-2*H*-chromene-3-carboxamide **40** using H_2O as *O*-nucleophile

As a further development of the methodology outlined in Scheme 5, path A, a new approach to 2-oxo-3-(5-aryl-1,3,4-oxadiazol-2-yl)-2*H*-chromenes of type **45** was elaborated [4e].



Scheme 10. Synthesis and rearrangement of 2-(*N*-aroylhydrazono)-2*H*-chromene-3-carboxamides **41** into 1,3,4-oxadiazolylchromenes **45**

As exemplified in Scheme 10 (path A), the procedure was based on the rearrangement of 2-(*N*-aroylhydrazono)-2*H*-chromene-3-carboxamides **41**, which are readily obtained by the reaction of 2-imino-2*H*-chromene-3-carboxamides **1** with benzohydrazide (**1 1**) in an acidic medium. Oxadiazolylchromene **45a** was also synthesized separately from amide-hydrazone **12** (*cf.* Scheme 2) by refluxing it in AcOH/H_2SO_4 mixture (Scheme 10, pat B). Furthermore, as part of our program on structure-activity relationship studies of different heterocycles as potential tyrosine kinase inhibitors [24], we were especially interested in a short and selective entry into heterocyclic compounds comprising 2-imino- or 2-oxo-2*H*-chromene and tetrahydrobenzo[*b*]thiophene moieties. In our synthetic approach to heterocycles of this type [4f,g] we also applied the approach summarized in Scheme 5, path A.

Conclusion

The results obtained in the study of the rearrangements of 2-imino-2*H*-chromene-3-carboxamides with different *N*-nucleophiles clearly indicate that the reactions studied follow the mechanisms described in Schemes 1 and 5. Finally, this work opened a new avenue for the synthesis of a variety of new 3-hetaryl substituted 2-oxo-2*H*-chromene derivatives.

Experimental

General

Melting points (°C) were measured on a Büchi melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60 F-254). ^{1}H-NMR spectra were recorded on Bruker WP-100 SY, Bruker DPX-250, Bruker AMX-400 or Varian WXR-400 spectrometers in DMSO-d_6 or DMSO-d_6–$CDCl_3$ using TMS as an internal standard (chemical shifts in δ ppm). Mass spectra (MS) were obtained with Finnigan MAT-4615B spectrometer at an ionization potential of 70 eV. Combustion analyses of all compounds synthesized gave satisfactory microanalytical data. Infrared spectra (IR) were recorded in KBr pellets on Nicolet Protege 460 FT-IR or an IBM 486 computer-controlled Specord M-80 spectrometers.

2-Imino-2*H*-chromene derivatives **1a–c** were prepared (**1a** (R = H; refs. [9,25]); **1b** (R = 6-OCH_3; ref. [26]); **1c** (R = 6-OH, 7-*n*-C_6H_{13}; ref. [4b]) by condensing cyanoacetamide with salicylaldehydes **9a–c** in ethanol at room temperature using piperidine as a catalyst to form the expected imino compounds **1a–c**.

(4-Oxo-3,4-dihydroquinazolin-2-yl)acetonitrile (**8**) [10], 2-oxo-2*H*-chromene-3-thiocarboxamide (**13**) [13], 1-amino-4,6-dimethyl-2(1*H*)-oxopyridine-3-carbonitrile (**15**) [27], (4-oxo-4*H*-3,1-benzoxazin-2-yl)acetonitrile (**33**) [22], ethyl 2'-carboxymalonanilate **37** [23] and salicylaldehyde **9c** [28] were prepared by known literature procedures.

Solvents were purified by conventional methods [29]. Starting materials, anthranilic acid (**2**), salicylaldehydes (**9a**,**b**), benzohydrazide (**11**), anthranilamide (**29**) and methyl anthranilate (**38**) were purchased from Aldrich®.

*2-(2-Oxo-2*H*-chromen-3-yl)quinazolin-4(3*H*)-one (***7a***):*

Method A: A mixture of **1a** (282 mg, 1.5 mmol) and anthranilic acid **2** (370 mg, 2.7 mmol) in dry and degassed toluene (10 mL) was refluxed for 5-6 h (TLC monitoring) through a column equipped with a Dean-Stark trap containing a thimble filled with 4Å molecular sieves which had been activated at 325 °C for 24 h. In the course of the reaction, ammonia was released. The mixture was cooled and a yellow precipitate was filtered off and recrystallized from DMF/BuOH to afford 205 mg (47%) of **7a**: M.p. 275-277 °C (lit. [5] m.p. 243 °C; lit. [6] m.p. 245 °C). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.49 (dddd, 1H, *J* = 8.3, 7.8, 0.6, 0.4 Hz, Ar*H*); 7.58 (m, 2H, Ar*H*); 7.79 (m, 2H, Ar*H*); 7.90 (m, 1H, Ar*H*); 8.03 (ddd, 1H, *J* = 7.7, 1.6, 0.4 Hz, Ar*H*); 8.18 (m, 1H, Ar*H*); 8.97 (s, 1H, *H-4*); 12.07 (br s, 1H, N*H*). IR (KBr), cm^{-1}: ν 3254 (NH), 1706 (C=O, lactone), 1690 (C=O, amide), 1606, 1579, 1553, 1465. MS (EI, 70 eV) *m/z* (rel.%): 290 ($M^{+\cdot}$, 83), 262 (17), 145 (8), 119 (100), 92 (19), 76 (5), 53 (10). Anal. Calcd for $C_{17}H_{10}N_2O_3$ (290.28): C, 70.34; H, 3.47; N, 9.65. Found: C, 70.29; H, 3.61; N, 9.79.

Method B: To a well stirred solution of quinazoline-2-acetonitrile **8** [10] (185 mg, 1 mmol) in propan-2-ol (5 mL) was added the equivalent amount of salicylaldehyde **9a** (0.1 mL) and a few drops of piperidine as a catalyst. The reaction mixture was stirred at room temperature for 2 h. The precipitated product was filtered off, washed with propan-2-ol and recrystallized from butan-1-ol to afford 214 mg (74%) of 2-(2-imino-2*H*-chromen-3-yl)quinazolin-4(3*H*)-one (**10a**): M.p. 225-228 °C. ^{1}H-NMR (100 MHz, DMSO-d_6): δ 7.22-7.28 (m, 2H, Ar*H*); 7.46 (dd, 1H, *J* = 8.3, 7.8 Hz, Ar*H*); 7.52-7.73 (m, 4H, Ar*H*); 8.14 (d, 1H, *J* = 7.8 Hz, Ar*H*); 8.96 (s, 1H, *H-4*); 8.98 (s, 1H, C=N*H*); 14.04 (br s, 1H, N*H*). IR (KBr), cm^{-1}: ν 3435 (NH), 3319 (NH), 3060, 1689 (C=O, amide), 1678 (C=N), 1655, 1599. MS (EI, 70 eV) *m/z* (rel.%): 289 ($M^{+\cdot}$, 76), 272 (100), 171 (10), 146 (30), 119 (62), 92 (19), 77 (6), 63 (9). A solution of the corresponding **10a** (189 mg, 0.65 mmol) in 10 mL of a mixture of ethanol/water/~32% hydrochloric acid (30:1:1, v/v/v) was refluxed with vigorous stirring for 1 h. After cooling to room temperature, the precipitated product was filtered off and recrystallized from DMF/BuOH to afford 169 mg (89%) of the title compound **7a**.

Method C: A solution of **30** (309 mg, 1.0 mmol) in glacial (99.8%) acetic acid (5 mL) was refluxed for 30 min. The mixture was cooled, the yellow precipitate was filtered off, washed with water and recrystallized from DMF/BuOH to afford 201 mg (70%) of **7a**. According to ^{1}H-NMR and IR spectral data as well as the melting points, the products obtained by *Methods A, B* and *C* are identical.

*2-(6-Methoxy-2-oxo-2*H*-chromen-3-yl)quinazolin-4(3*H*)-one (***7b***):*

Method A: The reaction of **1b** (327 mg, 1.5 mmol) was performed using the reaction conditions described for preparation of **7a** to give 187 mg (39%) of **7b**: ^{1}H-NMR (100 MHz, DMSO-d_6): δ 3.87 (s, 3H, OCH_3); 7.26-8.06 (m, 6H, Ar*H*); 8.18 (d, 1H, *J* = 8.0 Hz, Ar*H*); 8.99 (s, 1H, *H-4*); 12.00 (br s, 1H, N*H*). IR (KBr), cm^{-1}: ν 3242 (NH), 3065, 3010, 2971, 1706 (C=O, lactone), 1683 (C=O, amide), 1566, 1491. MS (EI, 70 eV) *m/z* (rel.%): 320 ($M^{+\cdot}$, 100), 292 (23), 277 (28), 249 (6), 221 (8), 146 (13), 119 (95), 90 (21), 76 (17). Anal. Calcd for $C_{18}H_{12}N_2O_4$ (320.31): C, 67.50; H, 3.77; N, 8.74. Found: C, 67.71; H, 3.81; N, 8.69.

Method B: The synthesis of **10b** was performed starting from **8** (185 mg, 1 mmol) and **9b** (0.15 mL) using the reaction conditions described for preparation of **10a** to give 227 mg (71%) of **10b**: ^{1}H-NMR (100 MHz, DMSO-d_6): δ 3.79 (s, 3H, OCH_3); 7.17 (s, 1H, Ar*H*); 7.41-7.93 (m, 5H, Ar*H*); 8.12 (d, 1H, *J* = 7.7 Hz, Ar*H*); 8.85 (s, 1H, *H-4*); C=N*H* and N*H* exchanged deuterium with the solvent. MS (EI, 70 eV) *m/z* (rel.%): 319 ($M^{+\cdot}$, 42), 302 (100), 276 (8), 259 (6), 222 (7), 160 (8), 146 (8), 119 (14). Subsequent acid hydrolysis of **10b** (160 mg, 0.5 mmol) employing the reaction conditions described for hydrolysis of **10a** afforded 130 mg (81%) of **7b**. According to ^{1}H-NMR, IR spectral data, and the melting points, the compounds obtained by *Methods A* and *B* are identical.

N^2-*Benzoyl-2-oxo-2*H-*chromene-3-carbohydrazonamide (***12***):*

Method A: A mixture of **1a** (188 mg, 1 mmol) and benzohydrazide (**11**) (136 mg, 1 mmol) in butan-1-ol (5 mL) was refluxed for 15–30 min (TLC monitoring) while ammonia was released. Then the mixture was cooled, the precipitate was filtered off and washed with hot ethanol to afford 267 mg (87%) of **12**: M.p. 187-189 °C. ^{1}H-NMR (100 MHz, DMSO-d_6): δ 6.87 (br s, 2H, NH_2); 7.40-7.90 (m, 9H, Ar*H*); 8.57 (s, 1H, *H-4*); 10.09 (br s, 1H, CON*H*). IR (KBr), cm^{-1}: ν 3418, 3181 (NH), 1704 (C=O, lactone), 1682 (C=O, amide), 1658 (C=N). Anal. Calcd for $C_{17}H_{13}N_3O_3$ (307.30): C, 66.44; H, 4.26; N, 13.67. Found: C, 66.09; H, 4.51; N, 13.89.

Method B: To a cold (0 °C) solution of 2-oxo-2*H*-chromene-3-carbothioamide **13** [13] (2.05 g, 10 mmol) in DMF (25 mL) dry acetone (15 mL) followed by iodomethane (2 mL, 32 mmol) were added. The mixture was kept for 24 h at a dark place. The hydroiodide precipitated was filtered off and washed with ether. Hydroiodide (10 mmol) was suspended in 1,4-dioxane (50 mL) and triethylamine (1.5 mL, 10 mmol) was added. After stirring for 1 h at room temperature, the solvent was removed under reduced pressure and the residue was extracted with $CHCl_3$ (2 x 10 mL). The extract was washed with ice water, dried over Na_2SO_4 and the solvent was removed *in vacuo* to afford 899 mg (41%) of *S*-methyl 2-oxo-2*H*-chromene-3-carboximidothioate (**14**) [30]: ^{1}H-NMR (250 MHz, DMSO-d_6): δ 2.47 (s, 3H, SCH_3); 7.11-7.83 (m, 4H, Ar*H*); 8.33 (s, 1H, *H-4*); 9.89 (s, 1H, N*H*). IR (KBr), cm^{-1}: ν 3247 (NH), 1729 (C=O, lactone), 1612 (C=N), 1593. The crude **14** was used without any purification in the

following stage. The imidothioester **14** (440 mg, 2 mmol) and benzohydrazide (**11**) (275 mg, 2 mmol) were dissolved in DMF/EtOH (3/1 mixture, 10 mL). The mixture was heated for 4 h at 80 °C until evolving methanethiol was detected. The solvents were removed under reduced pressure and the residue was washed with hot ethanol to afford 178 mg (29%) of **12**. According to ^{1}H-NMR, IR spectral data as well as the melting points, the compounds obtained by *Methods A* and *B* are identical.

N-*(3-Cyano-4,6-dimethyl-2(1*H*)-oxopyridin-1-yl)-2-oxo-2*H*-chromenes (***16***):*

Amidines **16a**,**b** were prepared from carbamoyliminochromenes **1a**,**b** and 1-aminopyridone **15** [27] using the reaction conditions described in *Method A* for the synthesis of **12**.

*1-[1-amino-1-(2-oxo-2*H*-chromen-3-yl)methylideneamino]-4,6-dimethyl-2(1*H*)-oxopyridine-3-carbonitrile (***16a***):*

Yield: 31%. M.p. 291-293 °C (dec.). ^{1}H-NMR (400 MHz, DMSO-d_6–$CDCl_3$): δ 2.29 (s, 3H, CH_3); 2.36 (s, 3H, CH_3); 6.38 (s, 1H, C*H*-pyridone); 7.46 (br s, 2H, NH_2); 7.48 (ddd, 1H, *J* = 7.7, 7.6, 1.0 Hz, *H-6*); 7.55 (dd, 1H, *J* = 8.4, 1.0 Hz, *H-8*); 7.78 (ddd, 1H, *J* = 8.4, 7.6, 1.4 Hz, *H-7*); 8.00 (dd, *J* = 7.7, 1.4 Hz, *H-5*); 8.74 (s, 1H, *H-4*). Anal. Calcd for $C_{18}H_{14}N_4O_3$ (334.33): C, 64.66; H, 4.22; N, 16.76. Found: C, 64.97; H, 4.34; N, 17.02.

*1-[1-amino-1-(6-methoxy-2-oxo-2*H*-chromen-3-yl)methylideneamino]-4,6-dimethyl-2(1*H*)-oxopyridine-3-carbonitrile (***16b***):*

Yield: 27%. M.p. 312-314 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 3H, CH_3); 2.37 (s, 3H, CH_3); 3.85 (s, 3H, OCH_3); 6.21 (s, 1H, C*H*-pyridone); 7.27 (dd, 1H, *J* = 9.1, 2.9 Hz, *H-7*); 7.34 (d, 1H, *J* = 2.9 Hz, *H-5*); 7.36 (d, 1H, *J* = 9.1 Hz, *H-8*); 7.46 (br s, 2H, NH_2); 8.89 (s, 1H, *H-4*). Anal. Calcd for $C_{19}H_{16}N_4O_4$ (364.35): C, 62.63; H, 4.43; N, 15.38. Found: C, 62.49; H, 4.58; N, 15.09.

*2-(Phenylimino)-2*H*-chromene-3-carboxamides* **30**, **31** and **39***:*

General procedure

To a stirred solution of anthranilates **29**, **2** or **38** (10 mmol) in glacial acetic acid (15 mL) was added an equivalent amount of the corresponding 2-imino-2*H*-chromene derivatives **1a**,**b**. The reaction mixture was stirred at room temperature overnight. The precipitated products were filtered off, washed with water, propan-2-ol (3 x 5 mL), and dried in air.

*2-[(2-Carbamoylphenyl)imino]-2*H*-chromene-3-carboxamide (***30***):*

Yield: 82%. M.p. 244-246 °C. ^{1}H-NMR (250 MHz, DMSO-d_6): δ 7.07-7.28 (m, 5H, CONH_2+Ar*H*); 7.40-7.64 (m, 3H, Ar*H*); 7.75-7.78 (m, 2H, CONH_2+Ar*H*); 7.83 (br s, 1H, CONH_2); 8.41 (s, 1H, *H-4*); 9.02 (br s, 1H, CONH_2). IR (KBr), cm^{-1}: ν 3392 (NH), 3168 (NH), 1640 (C=O+C=N), 1588. Anal. Calcd for $C_{17}H_{13}N_3O_3$ (307.30): C, 66.44; H, 4.26; N, 13.67. Found: C, 66.21; H, 4.39; N, 13.89.

*2-[(2-Carboxyphenyl)imino]-2*H*-chromene-3-carboxamide (***31***):*

Yield: 62%. M.p. 191-192 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.98 (d, 1H, *J* = 8.1 Hz, Ar*H*); 7.10-7.22 (m, 3H, Ar*H*); 7.41-7.48 (m, 2H, Ar*H*); 7.62 (br s, 1H, CONH_2); 7.64 (dd, 1H, *J* = 8.2, 0.6 Hz, Ar*H*); 7.90 (dd, 1H, *J* = 8.5, 0.6 Hz, Ar*H*); 8.42 (s, 1H, *H-4*); 9.21 (s, 1H, CONH_2). IR (KBr), cm^{-1}: ν 3300 (NH_2+OH), 3160 (NH), 1700 (C=O, acid), 1670 (C=O, amide). MS (EI, 70 eV) *m/z* (rel.%): 308 ($M^{+\cdot}$, 46), 291 (55), 264 (37), 248 (86), 220 (100), 189 (43), 173 (36), 145 (54), 119 (42), 89 (34), 65 (28), 44 (36). Anal. Calcd for $C_{17}H_{12}N_2O_4$ (308.30): C, 66.23; H, 3.92; N, 9.09. Found: C, 66.19; H, 4.01; N, 9.14.

*2-{[(2-Methoxycarbonyl)phenyl]imino}-2*H*-chromene-3-carboxamide (***39***):*

Yield: 68%. M.p. 214-217 °C. ^{1}H-NMR (250 MHz, DMSO-d_6): δ 3.71 (s, 3H, OCH_3); 6.98 (d, 1H, *J* = 8.0 Hz, Ar*H*); 7.17-7.26 (m, 3H, Ar*H*); 7.45-7.52 (m, 2H, Ar*H*); 7.73 (d, 1H, *J* = 8.2 Hz, Ar*H*); 7.76 (br s, 1H, CONH_2); 7.88 (d, 1H, *J* = 8.3 Hz, Ar*H*); 8.52 (s, 1H, *H-4*); 9.17 (br s, 1H, CONH_2). IR (KBr), cm^{-1}: ν 3424 (NH), 3272 (NH), 1716 (C=O, ester), 1688 (C=O, amide), 1608. Anal. Calcd for $C_{18}H_{14}N_2O_4$ (322.31): C, 67.07; H, 4.38; N, 8.69. Found: C, 66.79; H, 3.99; N, 8.43.

*2-(2-Oxo-2*H*-chromen-3-yl)-4*H*-3,1-benzoxazin-4-one (***32***):*

Method A: A solution of 2-[(2-carboxyphenyl)imino]-2*H*-chromene-3-carboxamide (**31**) (310 mg, 1 mmol) in acetic anhydride (3 mL) was refluxed for 30 min. After completed reaction, the mixture was cooled and the precipitate formed was filtered off, washed with water, cold propan-2-ol (2 x 5 mL) and recrystallized from benzene to give 224 mg (77%) of **32**: M.p. 203-204 °C (lit. [5] m.p. 197 °C; lit. [21b] m.p. 195 °C). ^{1}H-NMR (100 MHz, DMSO-d_6): δ 7.38-7.43 (m, 2H, Ar*H*); 7.65-7.74 (m, 3H, Ar*H*); 7.92-7.96 (m, 2H, Ar*H*); 8.20 (d, 1H, *J* = 7.9 Hz, Ar*H*); 8.86 (s, 1H, *H-4*). IR (KBr), cm^{-1}: ν 3063, 1749 (C=O), 1599. Anal. Calcd for $C_{17}H_9NO_4$ (291.26): C, 70.10; H, 3.11; N, 4.81. Found: C, 69.89; H, 3.34; N, 5.11.

Method B: 2-(2-Imino-2*H*-chromen-3-yl)-4*H*-3,1-benzoxazin-4-one (**34**) was synthesized from (4-oxo-4*H*-3,1-benzoxazin-2-yl)-2-acetonitrile (**33**) [23] (190 mg, 1 mmol) and 2-hydroxybenzaldehyde (**9a**) (0.1 mL) using the reaction conditions described in *Method B* for the synthesis of **10a** to give 177 mg

(61%) of iminochromene **34**. The compound **34** was used without any purification in the following reaction. Acid hydrolysis of **34** (130 mg, 0.45 mmol) employing the reaction conditions described for conversion of **10a** into **7a** afforded 77 mg (59%) of **32**. ^{1}H-NMR, IR spectral data, and melting points confirm identity of the compounds obtained by *Methods A* and *B*.

N-*aryl-2-oxo-2*H-*chromene-3-carboxamides* **36a**,**b***:*

General procedures

Method A: A mixture of **1a** or **1b** (1.5 mmol) and anthranilic acid **2** (275 mg, 2 mmol) in aqueous (80%) acetic acid (10 mL) was refluxed for 2 h. After the reaction finished, the mixture was cooled and the precipitate was filtered off, washed with water and cold propan-2-ol (2 x 5 mL). The products obtained were recrystallized from an appropriate solvent.

Method B: To a well stirred solution of ethyl 2'-carboxymalonanilate (**37**) [23] (4 mmol) in ethanol (10 mL) was added an equivalent amount of salicylaldehydes **9a** or **9b** and a few drops of piperidine as a catalyst. The reaction mixture was stirred at room temperature for ca. 1 day and then poured into water. The products precipitated were filtered off and recrystallized from an appropriate solvent.

N-*(2-Carboxyphenyl)-2-oxo-2*H-*chromene-3-carboxamide (***36a***):*

Yields: 82% (Method A) and 67% (Method B) (recrystallized from AcOH). M.p. 275-276 °C (lit. [5,21b] m.p. 279 °C). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.15 (dd 1H, *J* = 8.0, 8.0 Hz, Ar*H*); 7.39 (m, 2H, Ar*H*); 7.56 (dd, 1H, *J* = 8.0, 8.0 Hz, Ar*H*); 7.73 (dd, 1H, *J* = 7.9, 7.9 Hz, Ar*H*); 7.94 (d, 1H, *J* = 8.2 Hz, Ar*H*); 8.05 (d, 1H, *J* = 8.2 Hz, Ar*H*); 8.65 (d, 1H, *J* = 8.3 Hz, Ar*H*); 8.85 (s, 1H, *H-4*); 13.52 (br s, 1H, N*H*). IR (KBr), cm^{-1}: ν 3266 (NH), 3032 (CH), 1731 (C=O), 1696 (C=O), 1673 (C=O), 1608 (C=C). Anal. Calcd for $C_{17}H_{11}NO_5$ (309.28): C, 66.02; H, 3.58; N, 4.53. Found: C, 66.32; H, 3.78; N, 4.72.

N-*(2-Carboxyphenyl)-6-methoxy-2-oxo-2*H-*chromene-3-carboxamide (***36b***):*

Yields: 69% (Method A) and 59% (Method B) (recrystallized from butan-1-ol). M.p. 124-125 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.95 (s, 3H, OCH_3); 7.14-7.32 (m, 4H, Ar*H*); 7.42 (d, 1H, *J* = 8.2 Hz, Ar*H*); 8.01 (d, 1H, *J* = 8.0 Hz, Ar*H*); 8.60 (d, 1H, *J* = 8.0 Hz, Ar*H*); 8.89 (s, 1H, *H-4*); 13.20 (s, 1H, N*H*). IR (KBr), cm^{-1}: ν 3287 (NH), 2952 (CH), 1726 (C=O), 1694 (C=O), 1675 (C=O), 1614 (C=C). Anal. Calcd for $C_{18}H_{13}NO_6$ (339.31): C, 63.72; H, 3.86; N, 4.13. Found: C, 64.00; H, 4.03; N, 3.91.

*2-Oxo-2*H-*chromene-3-carboxamide (***25***):*

A solution of **39** (482 mg, 1.5 mmol) in aqueous (80%) acetic acid (10 mL) was refluxed for 2 h. After the reaction was complete, the mixture was cooled and the precipitate was filtered off, washed with water and cold propan-2-ol (5 mL). The product obtained was recrystallized from ethanol to give 228 mg (81%) of **25**: M.p. 279-280 °C (lit. [9] m.p. 280-282 °C). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.47 (ddd, 1H, *J* = 7.7, 7.7, 1.0 Hz, *H-6*); 7.53 (dd, 1H, *J* = 8.4, 1.0 Hz, *H-8*); 7.79 (ddd, 1H, *J* = 8.4, 7.7, 1.6 Hz, *H-7*); 7.96 (br s, 1H, CONH_2); 8.00 (dd, *J* = 7.7, 1.6 Hz, *H-5*); 8.12 (br s, 1H, CONH_2); 8.90 (s, 1H, *H-4*). Anal. Calcd for $C_{10}H_7NO_3$ (189.17): C, 63.49; H, 3.73; N, 7.40. Found: C, 63.54; H, 3.71; N, 7.51.

*2-oxo-3-(5-phenyl-1,3,4-oxadiazol-2-yl)-2*H*-chromene (***45a***):*

Method A: To a stirred solution of 2-imino-2*H*-chromene **1a** (1.88 g, 10 mmol) in glacial acetic acid (25 mL) was added an equivalent amount of benzohydrazide (**11**) (1.36 g, 10 mmol) and 2 drops of H_2SO_4. The reaction mixture was warmed to 40 °C and stirred at room temperature for *ca*. 3 h. The precipitated product was filtered off, washed with ethyl acetate (3 x 5 mL) and recrystallized from propan-2-ol to yield 2.82 g (92%) of 2-(*N*-benzoylhydrazono)-2*H*-chromene **41a**: M.p. 226-227 °C. ^{1}H-NMR (100 MHz, DMSO-d_6): δ 7.22-7.90 (m, 9H, Ar*H*); 7.98 (s, 1H, CONH_2); 8.23 (s, 1H, *H-4*); 9.16 (s, 1H, CONH_2); 11.25 (s, 1H, CON*H*). IR (KBr), cm^{-1}: ν 3305, 3238, 3110 (NH), 1698, 1678 (C=O), 1650 (C=N). A solution of benzoylhydrazonochromene **41a** (1.54 g, 5 mmol) in dry and degassed nitrobenzene (10 mL) was refluxed for 10–40 min. During the course of reaction, release of ammonia was observed. After reaction was completed (monitoring by TLC), the mixture was cooled and a precipitate was filtered off and recrystallized from benzene to give 1.13 g (78%) of 1,3,4-oxadiazolylchromene **45a** with m.p. 216-218 °C (lit. [31] m.p. 224 °C). ^{1}H-NMR (100 MHz, DMSO-d_6): δ 7.45-8.13 (m, 9H, Ar*H*); 9.02 (s, 1H, *H-4*). IR (KBr), cm^{-1}: ν 1744 (C=O). MS (EI, 70 eV) *m/z* (rel.%): 290 ($M^{+\cdot}$, 26), 262 (5), 206 914), 189 (12), 173 (32), 105 (100). Anal. Calcd for $C_{17}H_{10}N_2O_3$ (290.27): C, 70.34; H, 3.47; N, 9.65. Found: C, 70.27; H, 3.62; N, 9.73.

Method B: Benzoylcarbohydrazonamide **12** (*cf*. Scheme 2) (154 mg, 0.5 mmol) was refluxed in a mixture AcOH/H_2SO_4 (2 mL) for 15–30 min. After the reaction finished, the mixture was cooled and neutralized with aqueous ammonia. The precipitate formed was filtered off, washed with water and cold propan-2-ol (2 x 1 mL). The product obtained was recrystallized from an appropriate solvent to afford 112 mg (78%) of 1,3,4-oxadiazolylchromene **45a**. ^{1}H-NMR, IR spectral data, and melting points corroborate identity of the compounds obtained by *Methods A* and *B*.

*6-*n*-Hexyl-7-hydroxy-2-oxo-3-(5-phenyl-1,3,4-oxadiazol-2-yl)-2*H*-chromene (***45b***):*

1,3,4-Oxadiazolylchromene **45b** was prepared from carbamoyliminochromene **1c** [4b] and benzohydrazide (**11**) using the reaction conditions described in *Method A* for the synthesis of **45a**. Yield: 68%. M.p. 241-242 °C. ^{1}H-NMR (100 MHz, DMSO-d_6): δ 0.86 (t, 3H, J = 7.0 Hz, $CH_2(CH_2)_4CH_3$); 1.30 (m, 8H, $CH_2(CH_2)_4CH_3$); 1.56 (m, 2H, $CH_2(CH_2)_4CH_3$); 6.82 (s, 1H, *H-8*); 7.64 (m, 4H, Ar*H*); 8.09 (m, 2H, Ar*H*); 8.85 (s, 1H, *H-4*); 11.09 (br s, 1H, O*H*). IR (KBr), cm^{-1}: ν 3088 (OH), 2851 (CH_{alkyl}), 1744 (C=O), 1618 (C=C), 1570. Anal. Calcd for $C_{23}H_{22}N_2O_4$ (390.43): C, 70.75; H, 5.68; N, 7.17. Found: C, 70.81; H, 5.80; N, 7.22.

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Samples Availability: Available from the authors.