REARRANGEMENTS OF 2-IMINO-2H-1-BENZOPYRAN-3-CARBOXAMIDES UNDER ACTION OF ANTHRANILIC ACID AS *N*-NUCLEOPHILE

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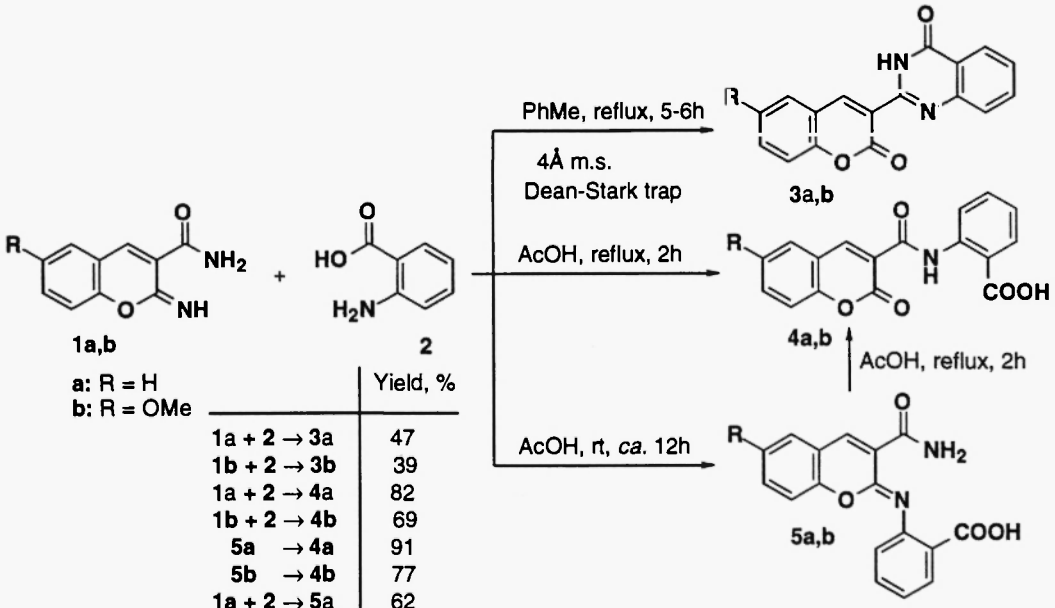
Abstract : New rearrangements of 2-imino-2H-1-benzopyran-3-carboxamides (**1**) under action of anthranilic acid (**2**) as *N*-nucleophile have been revealed. Starting from readily available 2-imino-2H-1-benzopyran-3-carboxamides (**1**) and anthranilic acid (**2**) and depending on reaction conditions, 2-(**2**-oxo-2H-1-benzopyran-2-yl)-3H-quinazolin-4-ones **3a.b** and 2-oxo-2H-1-benzopyran-3-(*N*-2-carboxyphenyl)carboxamides **4a.b** have been prepared *via* the rearrangements. Possible mechanisms of these rearrangements have been discussed.

Compounds comprising coumarin backbone (1-4) are of interest both for the range of pharmacological properties and for their chemistry. In view of the ubiquity of coumarin moiety in a variety of biologically active compounds, the synthesis of various analogs is important in gauging their potential as a source of chemotherapeutics. From the above line of reasoning we directed our research towards the development of a new procedures for synthesis of various coumarin derivatives (5-8) of biological interest.

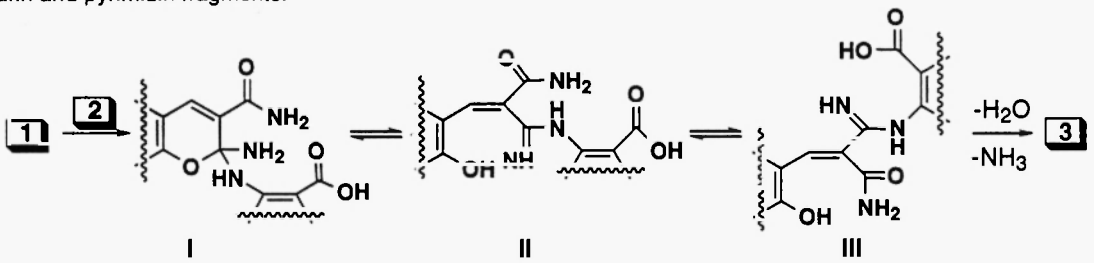
As part of our continuing studies (5) on reactivity of 3-substituted 2-imino-2H-1-benzopyrans under action of *N*-nucleophiles, we wish to report on "unusual" reactions of 2-imino-2H-1-benzopyran-3-carboxamides (**1**) with anthranilic acid (**2**) as a simple and efficient way to obtain different 2-oxo-2H-1-benzopyran derivatives *via* novel rearrangements (9). As shown in Scheme 1, either compounds **3** or **4** were formed (10) depending on reaction conditions. Refluxing of compounds **1a.b** (5,11) and **2** in degassed toluene afforded compounds **3a.b** (12) in moderate yields as only products. It is pertinent to note that strong liberation of ammonia was detected. A possible mechanism of coumarin and 4(3H)-quinazolinone moieties formation *via* a rearrangement of 2-imino-2H-1-benzopyran-3-carboxamides (**1**) under action of anthranilic acid (**2**) as *N*-nucleophile is shown in Scheme 2.



	Yield, %
1a + 2 → 3a	47
1b + 2 → 3b	39
1a + 2 → 4a	82
1b + 2 → 4b	69
5a → 4a	91
5b → 4b	77
1a + 2 → 5a	62
1b + 2 → 5b	81

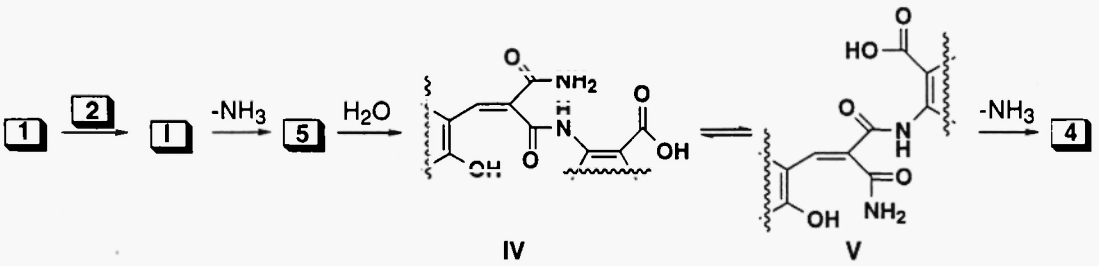
Scheme 1

It involves several steps: i) nucleophilic attack of NH_2 on C(2) of iminolactone ring (**1**+**2**→**I**); ii) iminolactone ring opening (**I**→**II**); and iii) E/Z isomerization of intermediate **II** (**II**→**III**) and subsequent cyclizations of intermediate **III** with formation of coumarin and pyrimidin fragments.



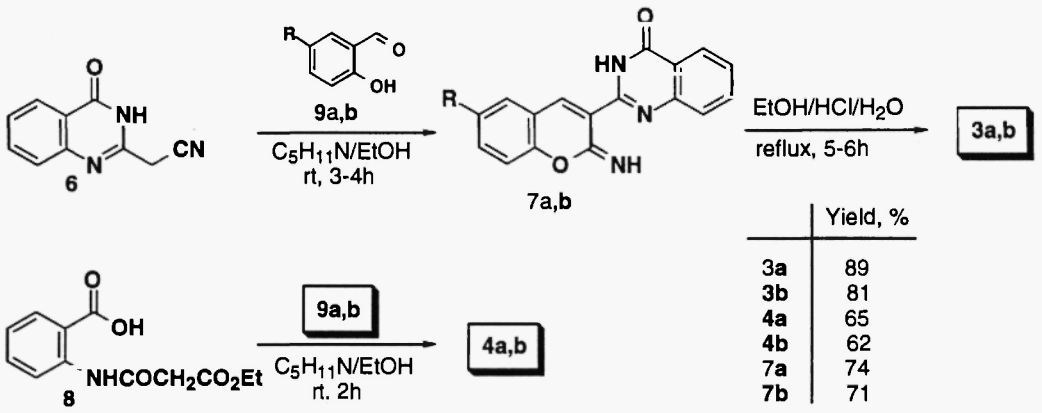
Scheme 2

Differently proceeded a reaction (Scheme 1) between compounds **1a.b** and **2** in aqueous acidic media (80% acetic acid). Refluxing for 2 hours in this solvent gave the other products of a rearrangement — 2-oxo-2H-1-benzopyran-3-(*N*-2-carboxyphenyl)carboxamides **4a.b** (13). A mechanism that accounts for the products **4a.b** is given in Scheme 3. Indeed, at room temperature reactions between **1** and **2** took place without iminolactone ring opening (5) and furnished intermediates **5** (14) which were converted into compounds **4** by further boiling.



Scheme 3

In order to fully characterize compounds **3** and **4** and to compare various methods (15) for coumarin and 4(3H)-quinazolinone moieties formation, we also synthesized compounds **3** and **4** *via* Knoevenagel condensation (17,18) of cyanomethylquinazolinone **6** (19) and *N*-acylanthranilic acid **8** (20) with salicylic aldehydes **9a.b** in ethanol and using piperidine as catalyst (Scheme 4).



	Yield, %
3a	89
3b	81
4a	65
4b	62
7a	74
7b	71

Scheme 4

In summary, new rearrangements of 2-imino-2H-1-benzopyran-3-carboxamides (**1**) were revealed. Depending on reaction conditions various 2-oxo-2H-1-benzopyran derivatives **3**, **4**, and **5** have been synthesized using 2-imino-2H-1-benzopyran-3-carboxamides (**1**) and anthranilic acid (**2**). Syntheses of compounds **3** and **4**, as described in Scheme 1, are new and efficient alternative routes to these 3-substituted coumarin derivatives utilizing simple precursors **1** and **2**.

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(9) Several manuscripts concerning the studies on rearrangements of 3-substituted 2-imino-2H-1-benzopyrans under action of *N*-nucleophiles are in progress and will appear in due course.

(10) All new compounds showed spectroscopic and analytical data consistent with assigned structures.

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(12) Typical procedure for synthesis of *2-(2-oxo-2H-1-benzopyran-2-yl)-3H-quinazolin-4-ones* (3): A mixture of **1a** (282 mg, 1.5 mmol) and anthranilic acid **2** (370 mg, 2.7 mmol) in 10 mL of dry and degassed toluene was refluxed for 5-6 hours (monitoring by TLC) with Dean Stark trap through a column containing a thimble filled with 4-Å molecular sieves which had been activated by being heated at 325°C for 24 h. During the reaction course, ammonia release was also observed. The mixture was cooled and yellow precipitate was filtered and recrystallized from DMF/BuOH to afforded 205 mg (47%) of the title compound **3a**: Mp 275-7 °C. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.49 (m, 1H, ArH); 7.58 (m, 2H, ArH); 7.79 (m, 2H, ArH); 7.90 (m, 1H, ArH); 8.03 (ddd, 1H, J = 7.7, 1.6, 0.4Hz, ArH); 8.18 (m, 1H, ArH); 8.97 (s, 1H, **H-4**); 12.07 (br s, 1H, **NH**). MS (EI, 70eV) *m/z* (r.i.): 290 (M^+, 83), 262 (17), 145 (8), 119 (14), 92 (100), 76 (5), 53 (10). IR (KBr), cm^{-1}: ν 3254m (NH), 1706s (C=O, lactone), 1690vs (C=O, amide), 1606m, 1579m, 1553s, 1465m. FW 290.28. Anal. Calcd. for $C_{17}H_{10}N_2O_3$: C 70.34; H 3.47; N 9.65. Found: C 70.29; H 3.61; N 9.79.

Compound **3b** was obtained similarly. Relevant data for **3b**: ^{1}H NMR (400MHz, DMSO-d_6): δ 3.87 (s, 3H, OCH_3); 7.26- 8.19 (m, 7H, Ar); 8.99 (s, 1H, **H-4**); 12.00 (br s, 1H, **NH**). MS (EI, 70eV) *m/z* (r.i.): 320 (M^+, 100), 292 (23), 277 (28), 249 (6), 221 (8), 146 (13), 119 (95), 90 (21), 76 (17). IR (KBr), cm^{-1}: ν 3242m (NH), 3065w, 3010w, 2971w, 1706s (C=O, lactone), 1683vs (C=O, amide), 1566s, 1491m. FW 320.31. Anal. Calcd. for $C_{18}H_{12}N_2O_4$: C 67.50; H 3.77; N 8.74. Found: C 67.71; H 3.81; N 8.69.

(13) For example: *2-Oxo-2H-1-benzopyran-3-(N-2-carboxyphenyl)carboxamide* **4a**: Mp 270-3 °C. ^{1}H NMR (400MHz, DMSO-d_6): δ 7.15 (dd 1H, J = 8.0, 8.0Hz ArH); 7.39 (m, 2H, ArH); 7.56 (dd, 1H, J = 8.0, 8.0Hz, ArH); 7.73 (dd, 1H, J = 7.9, 7.9Hz, ArH); 7.94 (d, 1H, J = 8.2Hz, ArH); 8.05 (d, 1H, J = 8.2Hz, ArH); 8.65 (d, 1H, J = 8.3Hz ArH); 8.85 (s, 1H, **H-4**); 13.52 (br s, 1H, **NH**). MS (EI, 70eV) *m/z* (r.i.): 309 (M^+, 27), 264 (10), 173 (100), 119 (26), 101 (27), 89 (22), 63 (10). IR (KBr), cm^{-1}: ν 3266m (NH), 1731s (C=O, lactone), 1696s (C=O, acid), 1673s (C=O, amide). FW 309.28. Anal. Calcd. for $C_{17}H_{11}NO_5$: C 66.02; H 3.59; N 4.53 Found: C 66.17; H 3.66; N 4.43.

(14) *2-((N-2-Carboxyphenyl)imino)-2H-1-benzopyran-3-carboxamide* **5a**: Mp 191-2 °C. ^{1}H NMR (400MHz, DMSO-d_6): δ 6.98 (d, 1H, J = 8.1Hz, ArH); 7.10-7.22 (m, 3H, ArH); 7.41-7.48 (m, 2H, ArH); 7.62 (s, 1H, NH_2); 7.64 (dd, 1H, J = 8.2, 0.6Hz, ArH); 7.90 (dd, 1H, J = 8.5, 0.6Hz, ArH); 8.42 (s, 1H, **H-4**); 9.21 (s, 1H, NH_2). MS (EI, 70eV) *m/z* (r.i.): 308 (M^+, 46), 291 (55), 264 (37), 248 (86), 220 (100), 189 (43), 173 (36), 145 (54), 119 (42), 89 (34), 65 (28), 44 (36). IR (KBr), cm^{-1}: ν 3300m (NH_2+OH), 3160w (NH), 1700s (C=O, acid), 1670s (C=O, amide). FW 308.30. Anal. Calcd. for $C_{17}H_{12}N_2O_4$: C 66.23; H 3.92; N 9.09. Found: C 66.19; H 4.01; N 9.14.

(15) Different methods (*cf.* ref. 16) for synthesis of various 3-(4-oxo-3,4-dihydro-2-quinazolinyl)-7-diethylamino-coumarin derivatives, which are structurally related to **3a.b**, have been reported. Namely, they have been prepared by reaction of 7-diethylaminocoumarin-3-carboxylic acid ethyl ester with anthranilamides; cyclization of 4-diethylaminosalicylaldehyde with 2-cyanomethyl-4(3H)-quinazolinones; of 7-amino-3-carbamoylcoumarins with isatoic anhydride; or of 4-diethylaminosalicylaldehyde with acetanilides and subsequent cyclization with H_2NCO_2Et and P_2O_5.

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