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2-Imino-2H-1-benzopyrans as Versatile Synthons in Heterocyclic Synthesis: Studies on Novel Rearrangements of 3-Substituted 2-Imino-2H-1-benzopyrans Under Action of *N*-Nucleophiles

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Abstract : A new chemoselective approach to synthesis of a series of 3-substituted coumarin derivatives and 6-substituted benzo[4,5]imidazo[1,2-*a*]quinolines was developed. It was based on novel rearrangements of different 3-substituted 2-imino-2H-1-benzopyrans 1 (2-imino-2H-1-benzopyran-3-carboxamide and 2-imino-3-(1H-benzoimidazol-2-yl)-2H-1-benzopyran) under action of *N*-nucleophiles. By using this methodology, two series of heterocyclic systems were synthesized, namely:

i) containing coumarin (2-oxo-2H-1-benzopyran) moiety substituted at C-3 position with different heterocycles such as 4H-1,2,4-triazole (7 and 10), 1,3,4-oxadiazole (8), 1,3,4-thiadiazole (9), 5-oxo-1,4-dihydro-benzo[*e*][1,2,4]triazepine (12), 1,1-dioxo-2H-benzo[*e*][1,2,4]thiadiazine (13), 4-oxo-3H-quinazoline (17), 4-oxo-5,6,7,8-tetrahydro-3H-benzo[4,5]thieno[2,3-*d*]pyrimidine (19), 1H-benzoimidazole (20), benzooxazole (21), benzothiazole (22), and
ii) comprising benzo[4,5]imidazo[1,2-*a*]quinoline backbone substituted at C-6 position with 1H-benzoimidazole (23) and benzooxazole (24) units.
Possible mechanisms of the revealed rearrangements were discussed and this approach is considered to be a new and efficient alternative route to a variety of heterocyclic compounds.

Keywords : rearrangements / coumarins / benzopyrans / imines / quinolines

Introduction

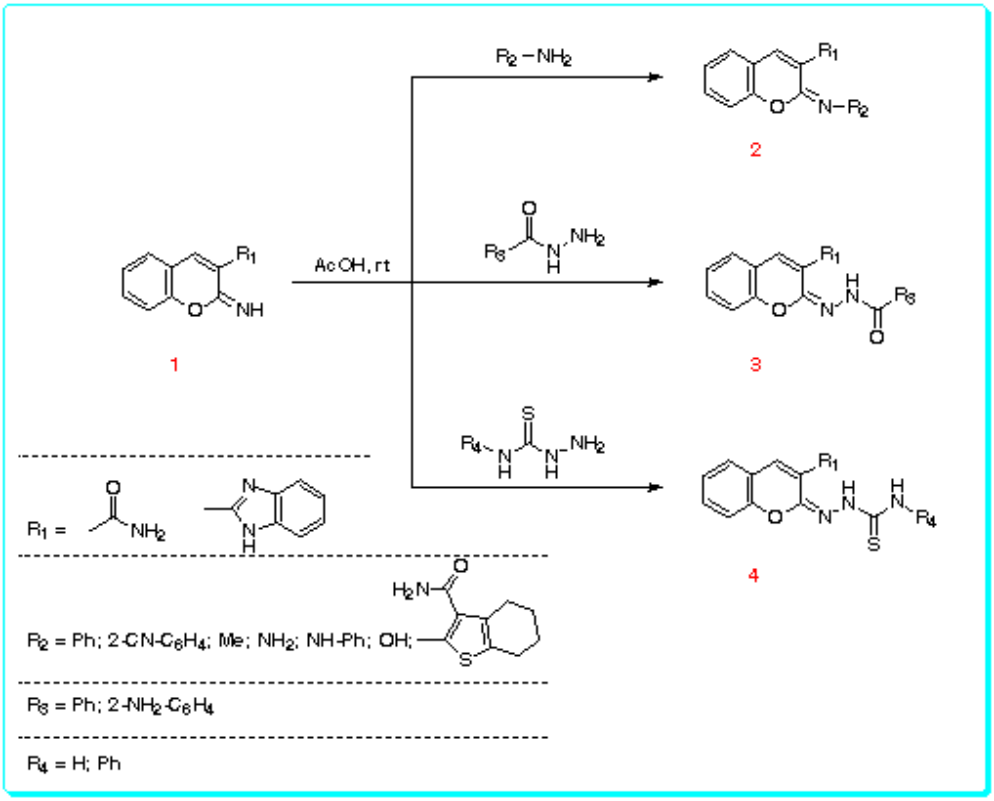
2-Iminocoumarins 1 (*cf.* Scheme 1) comprising 2H-1-benzopyran backbone are of our interest both for the range of pharmacological properties and for their chemistry [1]. In view of the ubiquity of 2H-1-benzopyran (2H-chromen) moiety in a variety of biologically active compounds, the synthesis of various analogs is important in gauging their potential as a source of chemotherapeutics. Taking into consideration the high

reactivity of different iminoesters towards *O*- and *N*-nucleophiles [1,2] and utilizing 3-substituted 2-imino-2H-1-benzopyrans of general structure 1 as readly available precursors, we directed our research to elaborate chemoselective procedures for synthesis a variety of heterocyclic compounds of biological interest containing 2H-1-benzopyran fragment tethered to different heterocycles.

Results and Discussion

As a result of our research we found that depending on reaction conditions 3-substituted 2-imino-2H-1-benzopyrans 1 reacted with different *N*-nucleophiles in two ways, namely, with iminolactone ring opening (Schemes 2-7) and without one (Scheme 1).
Indeed, in glacial acetic acid at ambient temperature reactions between 2-imino-2H-1-benzopyrans 1 and different primary amines took place without iminolactone ring opening and furnished 3-R_1-2-(R_2-imino)-2H-1-benzopyrans 2 [3] (Scheme 1). In a similar manner 2-imino-2H-1-benzopyran-3-carboxamide (1) (R_1 = $CONH_2$) reacted with arylhydrazides and thiosemicarbazides providing (Scheme 1) 2-((2-aminobenzoyl/benzoyl)hydrazono)-2H-1-benzopyran-3-carboxamides 3 (R_1 = $CONH_2$; R_3 = 2-NH_2-C_6H_4 or Ph) [4] and 2-(R_4-thiosemicarbazono)-2H-1-benzopyran-3-carboxamides 4 (R_1 = $CONH_2$; R_4 = H or Ph), respectively.
A mechanism that accounts for the products 2-4 may be analogous to acidic hydrolysis of 2-imino-2H-1-benzopyrans to the corresponding 2-oxo compounds (reaction with *O*-nucleophiles) and to comprehensively studied [2a] reactions of non-cyclic iminoesters with amines [2].

Scheme 1

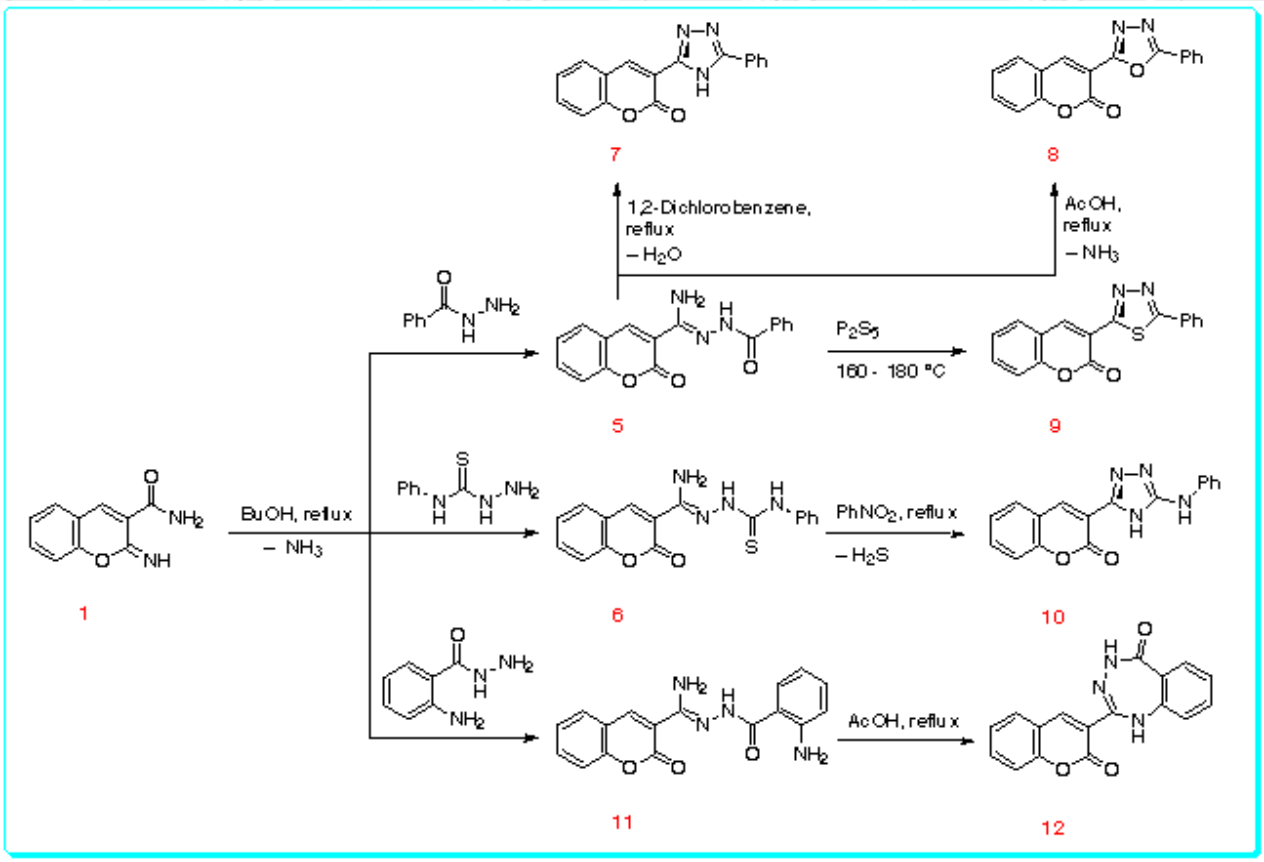


Refluxing of 2-imino-2H-1-benzopyran-3-carboxamide (1) with different hydrazides (benzoic hydrazide, 4-phenyl-3-thiosemicarbazide, and anthranilhydrazide) in butanol afforded (Scheme 2), respectively, amidrazones 5, 6 and 11 in good yields as only products. It is pertinent to note that strong liberation of ammonia was detected.
A possible mechanism of coumarin and carboxamidine fragments formation *via* a rearrangement of 2-imino-

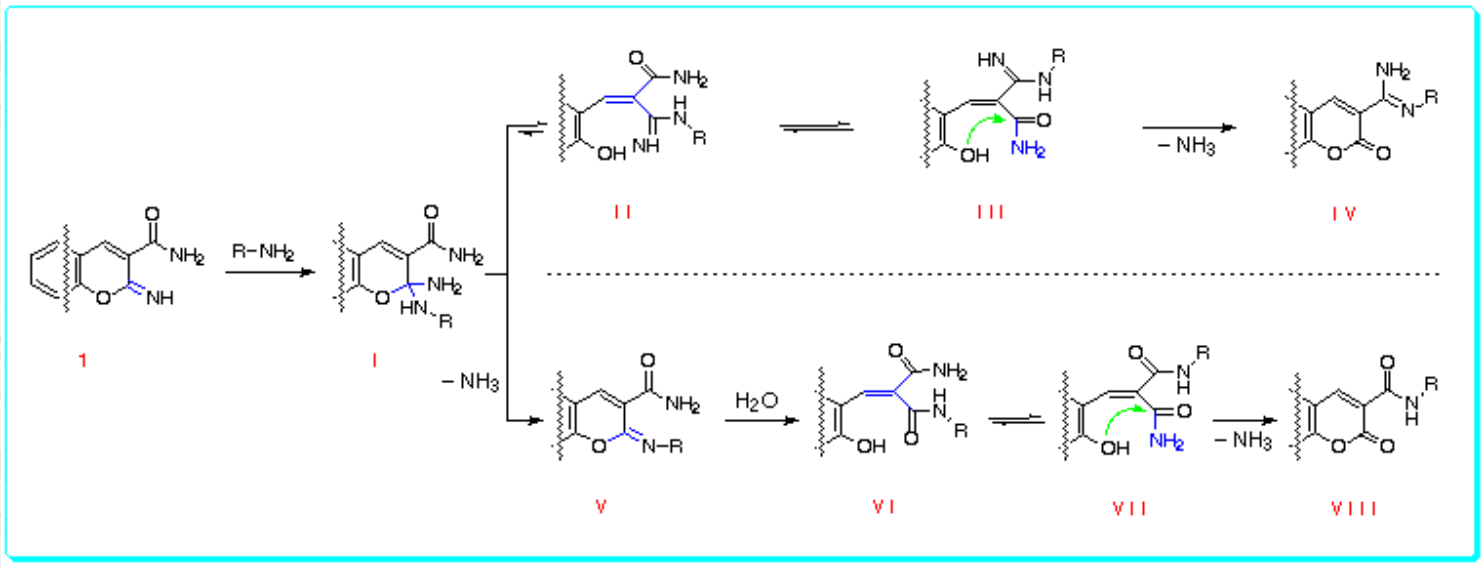
2H-1-benzopyran-3-carboxamide (1) under action of *N*-nucleophiles is shown in Scheme 3. It involves several steps: i) nucleophilic attack of NH_2 on C-2 of iminolactone ring (1 --> I); ii) iminolactone ring opening (I --> II); and iii) E/Z isomerization of intermediate II (II --> III) and subsequent cyclizations of intermediate III with formation of coumarin and carboxamidine fragments (IV). If a reaction is carried out in aqueous acidic media, an alternative mechanism (Scheme 3) might take place: i) formation of 2-(R-imino)-2H-1-benzopyrans (I --> V); i) nucleophilic attack of water on C-2 of iminolactone ring with simultaneous ring opening (V --> VI); iii) E/Z isomerization (VI --> VII) and subsequent cyclization of VII to form *N*-substituted 2-imino-2H-1-benzopyran-3-carboxamide of type VIII.

As indicated in Scheme 2, the variations of the reaction conditions induced the amidrazones obtained to undergo intramolecular cyclizations in different modes. It was shown that short-term refluxing of 2H-1-benzopyran-3-carboxylic acid N^1-benzoylamidrazone (5) in 1,2-dichlorobenzene afforded 2-oxo-3-(5-phenyl-4H-1,2,4-triazol-3-yl)-2H-1-benzopyran (7). If glacial acetic acid was used as a solvent, the formation of 2-oxo-3-(5-phenyl-1,3,4-oxadiazol-2-yl)-2H-1-benzopyran (8) was observed. In these reactions yields were moderate and not exceeded 35-40%. The alloying of 5 with phosphorus pentasulfide furnished 2-oxo-3-(5-phenyl-1,3,4-thiadiazol-2-yl)-2H-1-benzopyran (9) as major product in poor yield. Intramolecular cyclizations of amidrazones 6 and 11 (Scheme 2) yielded 2-oxo-3-(5-phenylamino-4H-1,2,4-triazol-3-yl)-2H-1-benzopyran (10) and 2-(2-oxo-2H-1-benzopyran-3-yl)-1,4-dihydro-benzo[*e*][1,2,4]triazepin-5-one (12), respectively.

Scheme 2

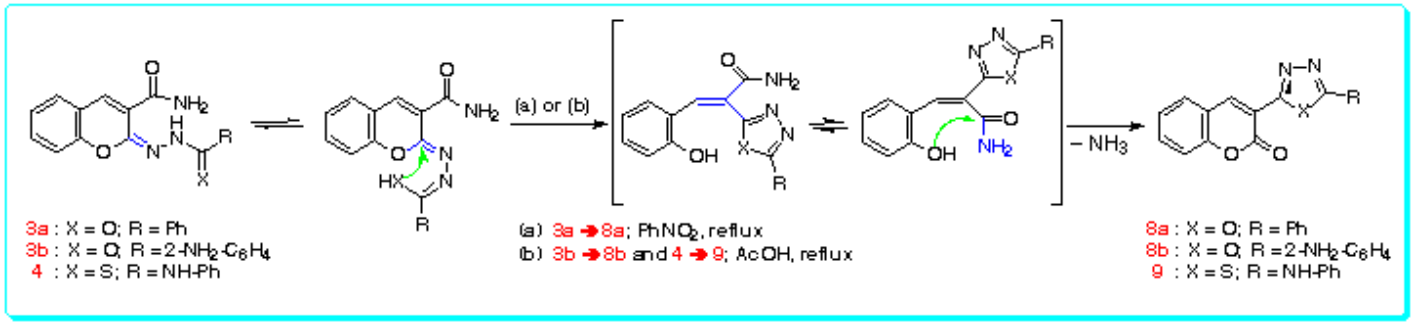


Scheme 3



It was also revealed that 2-(benzoylhydrazono)-2H-1-benzopyran-3-carboxamide (3a), 2-((2-aminobenzoyl)hydrazono)-2H-1-benzopyran-3-carboxamide (3b), and 2-(4-phenylthiosemicarbazono)-2H-1-benzopyran-3-carboxamide (4) had the capability to rearrange on refluxing in appropriate solvents (Scheme 4) to the corresponding 3-heterosubstituted 2-oxo-2H-1-benzopyrans: 2-oxo-3-(5-phenyl-1,3,4-oxadiazol-2-yl)-2H-1-benzopyran (8a), 2-oxo-3-(5-(2-aminophenyl)-1,3,4-oxadiazol-2-yl)-2H-1-benzopyran (8b) and 2-oxo-3-(5-phenylamino-1,3,4-thiadiazol-2-yl)-2H-1-benzopyran (9). A mechanism of these reactions is introduced in Scheme 4 as well. This approach to synthesis of the compounds 8a,b and 9 offers few advantages over the method of amidrazones 5, 6 and 11 intramolecular cyclizations as introduced in Scheme 2. In this case (Scheme 4) yields were good and desired heterocycles were obtained as sufficiently pure products.

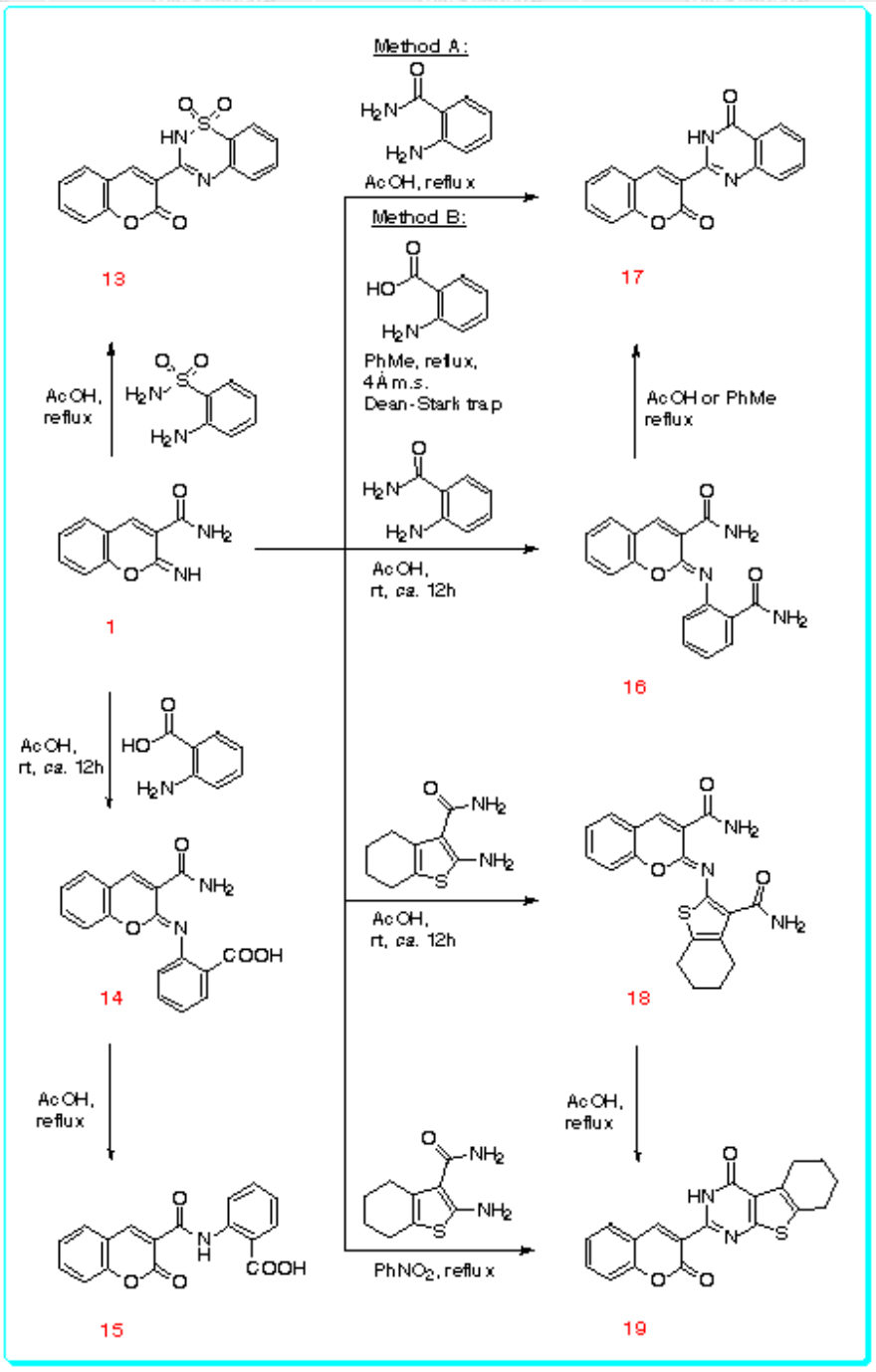
Scheme 4



Starting from our assumptions of two possible mechanisms of the rearrangements (Scheme 3, pathway A: II --> IV and pathway B: V --> VIII) and varying reaction conditions (aqueous acidic media - 80% acetic acid or solvents with high boiling points, *cf.* Schemes 5 and 6), we performed a number of experiments on rearrangements of 2-imino-2H-1-benzopyran-3-carboxamide (1) under action of different binucleophiles [5] such as 2-aminobenzenesulfonamide, anthranilic acid, anthranilamide, 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (Scheme 5) and 1,2-phenylenediamine, 2-aminophenol, 2-aminothiophenol (Scheme 6). At room temperature reactions between 1 and anthranilic acid, anthranilamide, or 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (Scheme 5) took place without iminolactone ring opening and furnished intermediates 14 (2-(3-carbamoyl-2H-1-benzopyran-2-ylideneamino)benzoic acid), 16 (2-(2-carbamoylphenylimino)-2H-1-benzopyran-3-carboxamide), and 18 (2-(3-carbamoyl-4,5,6,7-tetrahydro-benzo[*b*]thiophen-2-ylimino)-2H-1-benzopyran-3-carboxamide), respectively, which were converted into compounds 15 (2-((2-oxo-2H-1-benzopyran-3-carbonyl)amino)benzoic acid), 17 (2-(2-oxo-2H-1-benzopyran-3-yl)-3H-quinazolin-4-one), and 19 (2-(2-oxo-2H-1-benzopyran-3-yl)-5,6,7,8-tetrahydro-3H-

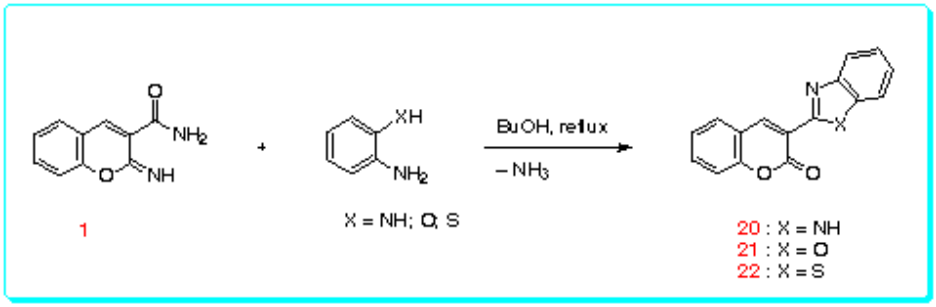
benzo[4,5]thieno[2,3-*d*]pyrimidin-4-one) by further boiling. 2-Oxo-(1,1-dioxo-1,2-dihydro-benzo[*e*][1,2,4]thiadiazin-3-yl)-2H-1-benzopyran (13) was synthesized directly from 1 and 2-aminobenzenesulfonamide without isolation of the corresponding imino product.

Scheme 5



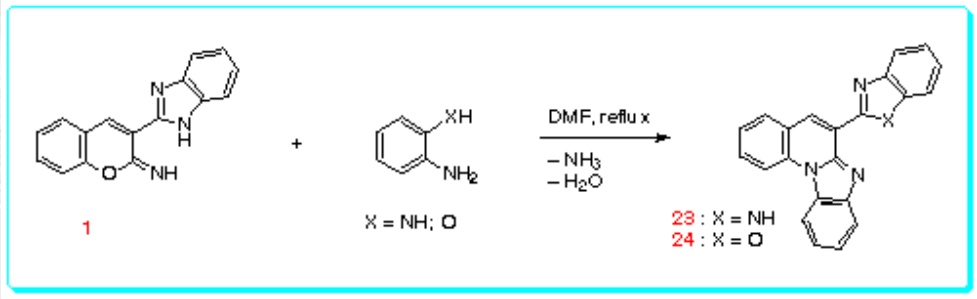
In a like manner (Scheme 6), 2-oxo-3-(1H-benzoimidazol-2yl)-2H-1-benzopyran (20), 2-oxo-3-(benzooxazol-2yl)-2H-1-benzopyran (21), and 2-oxo-3-(benzothiazol-2yl)-2H-1-benzopyran (22) were synthesized.

Scheme 6



6-(1H-Benzoimidazol-2-yl)benzo[4,5]imidazo[1,2-*a*]quinoline (23) and 6-benzooxazol-2-yl-benzo[4,5]imidazo[1,2-*a*]quinoline (24) were synthesized applying the same strategy based on rearrangements of 2-imino-2H-1-benzopyrans by the action of *N*-nucleophiles and starting from 2-imino-3-(1H-benzoimidazol-2-yl)-2H-1-benzopyran and 1,2-phenylenediamine or 2-aminophenol, as shown in Scheme 7.

Scheme 7



Conclusions

In summary, new chemoselective methods to synthesize a series of 3-heterosubstituted coumarin derivatives and 6-heterosubstituted benzo[4,5]imidazo[1,2-*a*]quinolines were developed. They were based on novel rearrangements of readily available 3-substituted 2-imino-2H-1-benzopyrans 1 (2-imino-2H-1-benzopyran-3-carboxamide and 2-imino-3-(1H-benzoimidazol-2-yl)-2H-1-benzopyran) under action of different *N*-nucleophiles.

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Biographical sketch

Yaroslav V. Bilokin was born in Kharkov (Ukraine) in 1969, and received his *MSc* degree from Kharkov State University, in 1993, for work in synthesis of heterocycles containing coumarin unit. He subsequently joined Department of Organic Chemistry of Ukrainian Academy of Pharmacy, in 1993, helding a Reserch Scientist position for three years.
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