One-Pot Microwave-Assisted Synthesis of a Benzopyrano[2,3-c]pyrazol-3(2*H*)-one Library

Alexander V. Borisov,*[,†] Nikolay Yu. Gorobets,[‡,§] Sergey A. Yermolayev,[‡] Irina O. Zhuravel',[†] Sergiy M. Kovalenko,[†] and Sergey M. Desenko[‡]

National University of Pharmacy, Pushkinska str. 53, 61002 Kharkiv, Ukraine, and Department of Chemistry of Heterocyclic Compounds, SSI "Institute for Single Crystals" of National Academy of Sciences of Ukraine, Lenin Ave 60, 61001 Kharkiv, Ukraine

Received May 31, 2007

Modern methodology applies the reactivity of 2-iminocoumarine (2-imino-2*H*-chromene) derivatives in reaction with different nucleophiles[1] and electrophiles[2] for construction of heterocyclic systems containing the coumarine (benzopyrane, 2*H*-chromen-2-one) moiety. The products of these reactions are used as bioactive compounds[3] or luminescent dyes[4] for different needs. In continuation of our works[2] on utilization of the 2-iminocoumarine reactivity for the synthesis of diverse benzopyranes fused with nitrogen containing heterocycles, here, we present a facile one-pot microwave-assisted protocol for fast generation of a benzopyrano[2,3-*c*]pyrazol-3(2*H*)-one library.

Initially the simplest benzopyrano[2,3-*c*]pyrazol-3(2*H*)-one was isolated from a complex reaction mixture by O'Callaghan.[5] Afterwards, some other synthetic methods for this compound and its 3-thioanalogue were published.[6] Thus, a reaction of substituted 1*H*-pyrazol-5(4*H*)-ones with 4-dialkylaminosalicylic aldehydes was proposed for the synthesis of 7-dialkylaminobenzopyrano[2,3-*c*]pyrazol-3(2*H*)-ones substituted in the pyrazolone ring.[7] However, all the published reactions cannot be used for fast generation of the desired benzopyrano[2,3-*c*]pyrazol-3(2*H*)-one combinatorial library. They are limited by low overall yield and restricted diversity of the final products.

In our previous work,[8] a representative of the compounds **4***{12,10}* was isolated as a side product of acetylation of hydrazonocoumarine **3***{12,10}* in the medium of acetic anhydride under reflux conditions during 15 min (Scheme 1). The same compound **4***{12,10}* was also obtained as the only product from the hydrazone **3***{12,10}* in refluxing DMF during 36 h. Addition of 2.0 equiv of the acetic anhydride to the reaction mixture was shown to decrease the reaction time to 6 h without formation of the diacetilated product **5** (Scheme 1). Thus, the presence of the acetic anhydride assisted the desamination of the hydrazone **3***{12,10}* into the benzopyrano[2,3-*c*]pyrazol-3(2*H*)-one **4***{12,10}*.

Due to the long reaction time (6–36 h), the reaction described above (Scheme 1) can not be carried out in high-throughput format for fast generation of a combinatorial library.

To improve this method, we applied the technology of microwave-assisted organic synthesis. This technology is now widely used for fast generation of combinatorial libraries in automated and parallel synthesis.[9] Initially, we chose the starting unsubstituted hydrazone **3***{1,3}* to find the optimal conditions for the desamination process. We varied the DMF–acetic anhydride ratio, reaction time, and temperature under microwave irradiation and established that the optimal conditions are 2.5 equiv of the Ac_2O in 1 mL of DMF, 200 °C, and 10 min and the maximal HPLC yield of the desired product **4***{1,3}* is only 66%. However, the HPLC analysis of the final reaction mixture indicated also a formation of several by-products that could be caused by side acetylation reactions. Moreover, the presence of the acetic anhydride makes it impossible to apply starting compounds containing reactive substituents such as OH or COOH groups (e.g., building blocks **1***{7}, {10}, {11}*, and **2***{6}*). The possibility to introduce these substituents into the final molecule is important regarding future diversification of the benzopyrano[2,3-*c*]pyrazol-3(2*H*)-one scaffold.

Thus, we switch over to a search for such reaction conditions that could exclude the acetic anhydride. Applying acetic acid as a reaction medium under microwave irradiation at 190 °C for 5 min led to a full conversion of the starting hydrazone **3***{1,3}* into the desired benzopyrano[2,3-*c*]pyrazol-3(2*H*)-one **4***{1,3}* (Scheme 2) with a small level of byproducts in the final reaction mixture. Moreover, we have succeeded in carrying out this transformation in one pot starting from the 2-iminocoumarine-3-carboxamide **1***{1}* and the phenyl hydrazine under the same conditions. Thus, in the final protocol, we applied 1.50 mmol of the starting 2-iminocoumarin-3-carboxamide **1** and 5% excess of the hydrazine **2** in 4.5 mL of the acetic acid under microwave irradiation at 190 °C for 5 min. The compounds **4***{7,3}* and **2***{2,6}* containing OH and COOH groups correspondingly were also synthesized in larger scale in 19 mL of the acetic acid using 6.0 mmol of the parent iminocoumarins **1**, the

Table 1. Representative Library Members (Isolated Yields and Purity)

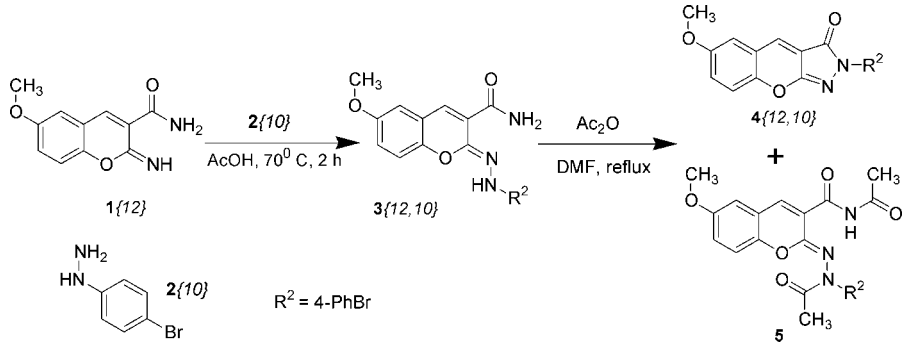
entry	R^1	R^2	isolated yield (%)	purity (HPLC, %)
4*{1,3}*	H	H	72	98
4*{1,7}*	H	4-NO_2-Ph	85	90
4*{1,9}*	H	4-OMe-Ph	70	94
4*{1,10}*	H	4-Br-Ph	74	95
4*{2,3}*	8-OMe	H	80	98
4*{2,6}*	8-OMe	4-COOH-Ph	79, 87*a*	99
4*{2,2}*	8-OMe	Bn	52	98
4*{3,3}*	8-OEt	H	61	>99
4*{5,2}*	6-Cl	Bn	65	97
4*{5,1}*	6-Cl	t-Bu	49	89
4*{7,3}*	7-OH	H	42, 43*a*	>99
4*{10,3}*	6-t-Bu-8-OH	H	52	98

[a] Scale-up protocol.

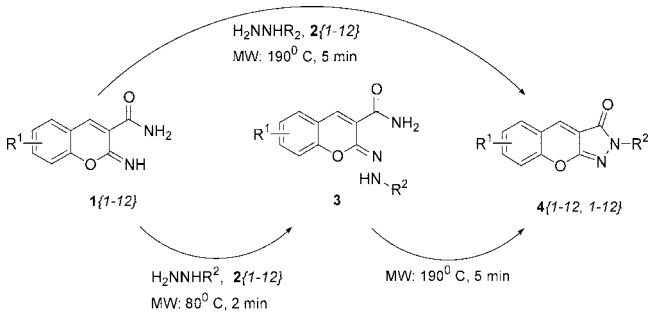
* Corresponding author. E-mail: borisov@onet.com.ua.
† National University of Pharmacy.
‡ SSI "Institute for Single Crystals" of National Academy of Sciences of Ukraine.
§ E-mail: gorobets@isc.kharkov.com. Fax: +38(057)3409343.

10.1021/cc700090c CCC: $37.00
Published on Web 08/30/2007

Scheme 1. Described Synthesis of the Benzopyrano[2,3-*c*]pyrazol-3(2*H*)-ones



Scheme 2. Generation of the Benzopyrano[2,3-*c*]pyrazol-3(2*H*)-one Library **4** and Representatives of Hydrozones **3**



same excess of the corresponding hydrazine **2**, and the reaction temperature (190 °C), but applying a slightly longer time of irradiation (10 min). Application of the larger scale conditions provided also higher isolated yields for the compounds **4***{7,3}* and **2***{2,6}* (see Table 1).

In the contrast to use of the acetic anhydride in such methodology, acceleration of the desamination process is achieved by application of high reaction temperature conditions in the acidic acid medium. Under much milder conditions (irradiation with microwaves at 80 °C for 5 min), the hydrazone **3** was formed as an individual product (Scheme 2).

We then synthesized a 144-member library demonstrating the use of microwave irradiation in a monomode reactor (EmrysTM Creator EXP, Biotage) as a simple and effective method for the rapid preparation of the compounds **4** in good

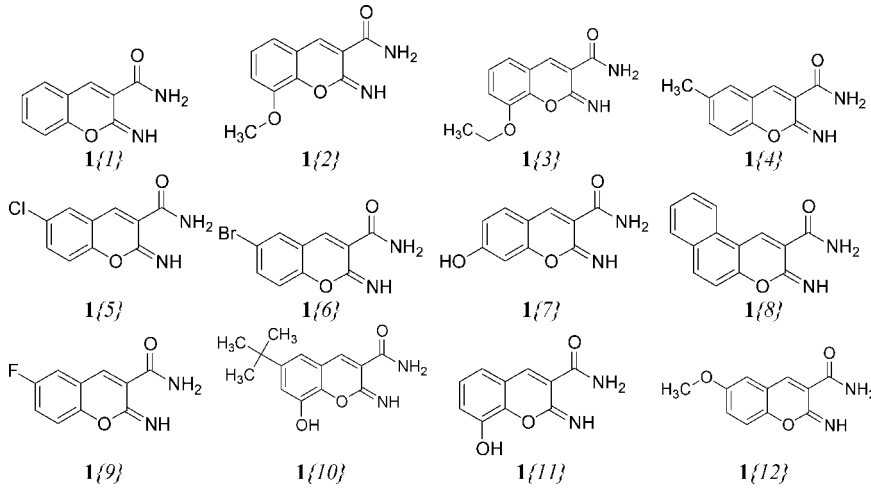


Figure 1. Selected 2-iminocoumarin-3-carboxamides **1***{1–12}* for library design.

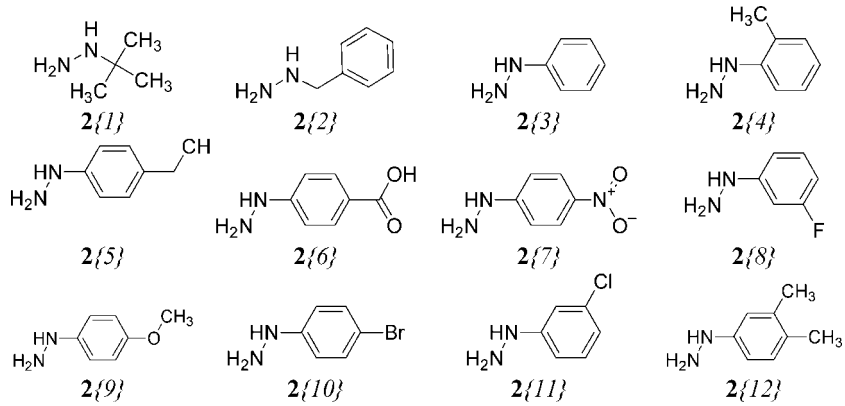


Figure 2. Selected hydrazines **2***{1–12}* for library design.

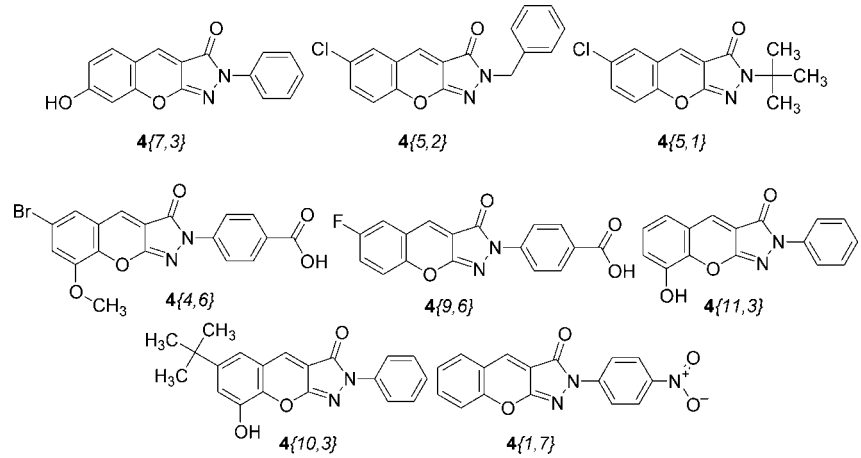


Figure 3. Examples of the synthesized benzopyrano[2,3-*c*]pyrazol-3(2*H*)-ones **4**.

average isolated yield and excellent purities for most cases (see Table 1 and the Supporting Information for details).

In the event, the library containing the core structure **4** was prepared in one synthetic operation using our standard microwave-assisted (AcOH, 190 °C, 5 min), one-pot reactions from the commercially available starting hydrazines **2** and 2-iminocoumarin-3-carboxamides **1** which can be easily synthesized (see Figures 1 and 2).[1]

Applying this method, it was also possible to synthesize the benzopyrano[2,3-*c*]pyrazoles **4** containing hydroxy or carboxy groups (see Figure 3). Such derivatives can be applied for further diversification of the benzopyrano[2,3-*c*]pyrazol-3(2*H*)-one scaffold.

In summary, we have developed a facile microwave-assisted protocol for fast generation of a 2-arylbenzopyrano[2,3-*c*]pyrazol-3-one library **4** utilizing highly reactive 2-iminocoumarines **1** and the corresponding hydrazines **2** as starting materials. High-reaction-temperature reaction conditions achieved by microwave irradiation in the acetic acid allowed the synthesis to be carried out in one pot to obtain the desired compounds (144 library members) in 43–87% isolated yields and 90–100% purity (HPLC). The reaction scale-up required a longer time of microwave irradiation but gave the products in higher isolated yields. The library members containing carboxy and hydroxy groups may be used in the future for additional diversification of the benzopyrano[2,3-*c*]pyrazol-3-one scaffold.

Acknowledgment. The authors acknowledge Dr. Alexandre V. Ivachtchenko (Chemical Diversity Laboratories, Inc.) for financial support of our work. We also thank to our colleagues, Dr. Aleksey Silin and Prof. Viktor Nikitchenko, for valuable dissections of the work results.

Supporting Information Available. Synthesis details, LC/MS, ^{1}H NMR, ^{13}C NMR, and IR data for compounds **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Kovalenko, S. M.; Bylov, I. E.; Sytnik, K. M.; Chernykh, V. P.; Bilokin, Y. V. *Molecules* **2000**, *5*, 1146. (b) Bilokin, Y. V.; Vasylyev, M. V.; Branytska, O. V.; Kovalenko, S. M.; Chernykh, V. P. *Tetrahedron* **1999**, *55*, 13757. (c) Gorobets, N. Yu.; Borisov, A. V.; Silin, A. V.; Nikitchenko, V. M.; Kovalenko, S. N *Chem. Heterocycl. Comp.* **2002**, *38*, 1389. (d) Briel, D.; Leistner, S.; Wagner, G. *Synthesis* **1986**, 147.

(2) (a) Borisov, A. V.; Dzhavakhishvili, S. G.; Zhuravel, I. O.; Kovalenko, S. M.; Nikitchenko, V. M. *J. Comb. Chem.* **2007**, *9*, 5. (b) Gorobets, N. Yu.; Abakumov, V. V.; Borisov, A. V.; Nikitchenko, V. M. *Chem. Heterocycl. Comp.* **2002**, *40*, 334. (c) Fadda, A. A.; Zeimaty, M. T.; Gerges, M. M.; Refat, H. M.; Biehl, E. R. *Heterocycles* **1996**, *43*, 23.

(3) (a) Ukhov, S. V.; Kon'shin, M. E.; Odegova, T. F. *Pharm. Chem. J.* **2001**, *35*, 364. (b) Bylov, I. E.; Vasylyev, M. V.; Bilokin, Y. V. *Eur. J. Med. Chem.* **1999**, *34*, 997. (c) Hadfield, J. A.; Pavlidis, V. H.; Perry, P. J.; McGown, A. T. *Anti-Cancer Drugs* **1999**, *10*, 591.

(4) (a) Maslov, V. V.; Gorobets, N. Yu.; Borisov, A. V.; Nikitchenko, V. M. *J. Appl. Spectrosc.* **2003**, *70*, 794. (b) Yu, J.; Shirota, Y. *Chem. Lett* **2002**, 984. (c) Rajagopal, R.; Shenoy, V. U.; Padmanabhan, S.; Sequeira, S.; Seshadri, S. *Dyes Pigments* **1990**, *13*, 167. (d) Asimov, M. M.; Nikitchenko, V. M.; Novikov, A. I.; Rubinov, A. N.; Bor, Z.; Gaty, L. *Chem. Phys. Lett.* **1988**, *149*, 140.

(5) O'Callaghan, C. N. *J. Chem. Soc. Perkin Trans.* **1980**, *1*, 1335.

(6) (a) Khodairy, A. *Synth. Commun.* **2001**, *31*, 2697. (b) Abd Allah, O.A. *Il Farmaco* **2000**, *55*, 641. (c) El-Sayed, A. M.; Ghattas, A.-B. A. G.; El-Wassimy, M. T.; Abd Allah, O. A. *Il Farmaco* **1999**, *54*, 56.

(7) Fuerstenwerth, H. DE Patent 3627744 A1, 1988.

(8) Gorobets, N. Yu.; Ermolaev, S. A.; Silin, A. V.; Nikltchenko, V. M. *Visnik Kharkivs'kogo Natsional'nogo Universitetu im. V. N. Karazina* **2002**, *573*, 62.

(9) Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250.

CC700090C