ORGANIC LETTERS

2008
Vol. 10, No. 20
4473−4476

Synthesis of Highly Functionalized 2(1*H*)-Pyrazinone 3-Carboxamide Scaffolds

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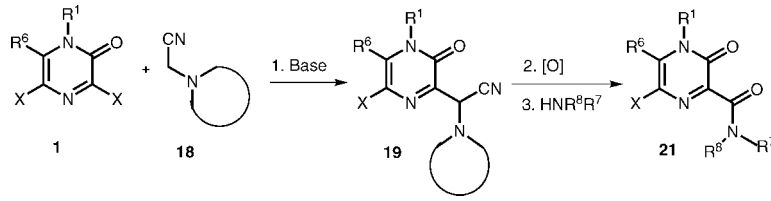
Received July 22, 2008

ABSTRACT



Synthesis of highly functionalized 2(1*H*)-pyrazinone 3-carboxamide derivatives is reported. A one-pot, two-step process including the base-mediated reaction of N,N-disubstituted aminoacetonitrile derivatives 18 with 3,5-dihalo-2(1*H*)-pyrazinones 1 afforded substituted aminoacetonitrile pyrazinone derivative 19, which on subsequent oxidation followed by transamidation of the resulting intermediate with primary or secondary amines gave the corresponding highly functionalized 2(1*H*)-pyrazinone 3-carboxamide derivatives 21.

Since 1983, 3,5-dihalo-2(1*H*)-pyrazinones **1** have proven to be versatile scaffolds in organic synthesis,[1] and an efficient synthesis for 3,5-dihalo-2(1*H*)-pyrazinones has been developed in our laboratory.[2] Different methods have been studied to functionalize this heterocyclic scaffold[1,3] which can now be functionalized with various substituents.

One of the functionalizations that was so far not straightforward to achieve was the functionalization of the 3-position with a carboxamide function (scaffold 2, Figure 1). This scaffold drew our attention in the framework of peptidomimetic research going on in the group.

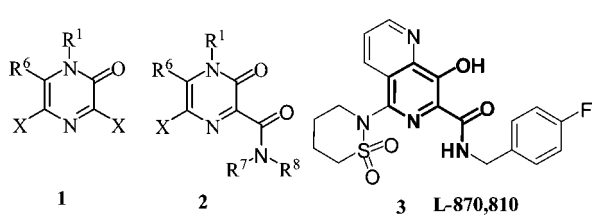


Figure 1. 3,5-Dihalo-2(1*H*)-pyrazinone **1**, pyrazinone with carboxamide function **2**, and Merck's L-870810 integrase inhibitor **3**.

This pyrazinone scaffold has the ability to stabilize peptide conformations (e.g., β-sheet and β-turn) or reduce the peptidyl features of peptide-like compounds.

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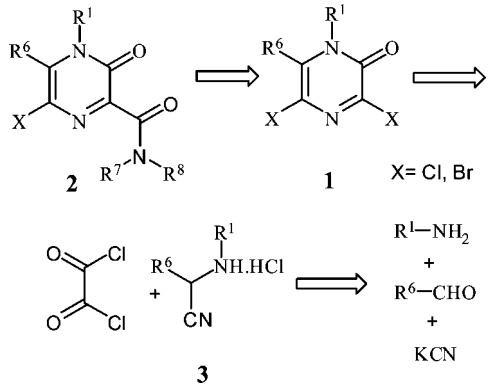
10.1021/ol801664v CCC: $40.75
Published on Web 09/18/2008

Similar pyrazinone scaffolds have been used successfully in tryptase inhibitors,[4] thrombin inhibitors,[5−7] and caspase-3 inhibitors.[8]

These pyrazinones have very interesting structural similarity with Merck's L-870810 integrase inhibitor (**3**)[9,10] as shown in Figure 1.

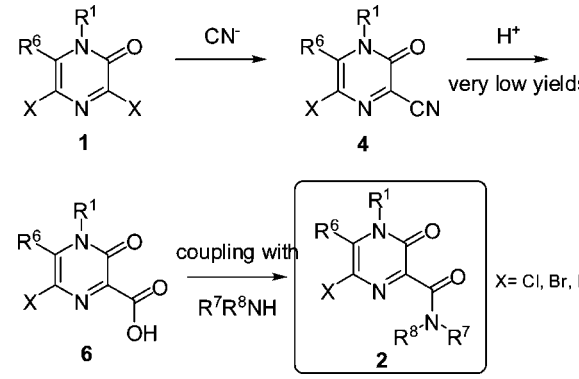
To synthesize this pyrazinone scaffold **2**, we wanted to use 3,5-dihalo-2(1*H*)-pyrazinones **1** as the starting point since this synthesis should allow us to introduce diverse substituents at different positions of the scaffold **2**. A variety of R^1 and R^6 substituents of scaffold **2** could be introduced while synthesizing pyrazinone **1** (Scheme 1). Moreover, the appropriate halogen atom at position 5 could allow us to introduce different substituents by using palladium-catalyzed reactions,[3] and this synthetic route could be very useful to synthesize a focused library of druglike compounds.

Scheme 1. Retrosynthesis of Pyrazinone Scaffold **2**



A general way to get this carboxamide functionality at position 3 of pyrazinones **1** is the insertion of a cyano group followed by hydrolysis of the cyano group and the coupling of an amine with the resulting carboxylic acid (Scheme 2). The hydrolysis of the cyano group to the pyrazinone carboxylic acid **6**, however, is a very low yielding synthetic step in our experience.

Scheme 2. General Synthesis of Pyrazinone Derivative **2**



Thus, it was necessary to develop a new and more efficient method which would provide us with carboxamidepyrazinone scaffold **2**.

In the case of 3,5-dihalo-2(1*H*)-pyrazinones **1**, we could take advantage of the highly electrophilic C3 carbon of pyrazinone **1**. Thus, we envisioned the insertion of carboxamide at C3 by using the "umpolung concept" which could lead us to generate pyrazinone scaffold **2** directly from dihalopyrazinone **1**. This could be achieved by applying the well-known Stork method.[11]

Our first attempt was the use of N,N-disubstituted aminoacetonitrile derivative **7** as a synthon for amides of general composition **8 (**Figure 2**)**. The two-step process[12]consisting of a base-mediated alkylation of the methylene moiety by S_NAr (addition−elimination) at the highly electrophilic position C-3 of dihalo 2(1*H*)-pyrazinone and subsequent oxidation could result in the generation of the desired carboxamidopyrazinone **2** after elimination of HCN from an intermediate cyanohydrine generated from **9** (Scheme 3).[13]

Figure 2. *N*,*N*-Disubstituted aminoacetonitrile derivative **7** as a synthon for amide of general composition **8**.

During the optimization of the method to provide a general reaction procedure, KHMDS was found to be a suitable base and −78 °C was found to be the temperature of choice that offered a clean reaction as compared to NaH or NaHMDS at room temperature or at lower temperature (0 to −78 °C). When the oxidant Na_2O_2 is used, the product **13a** was isolated in 16% yield only (Table 1).

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Scheme 3. First Attempt To Synthesize Pyrazinone Derivative **2**

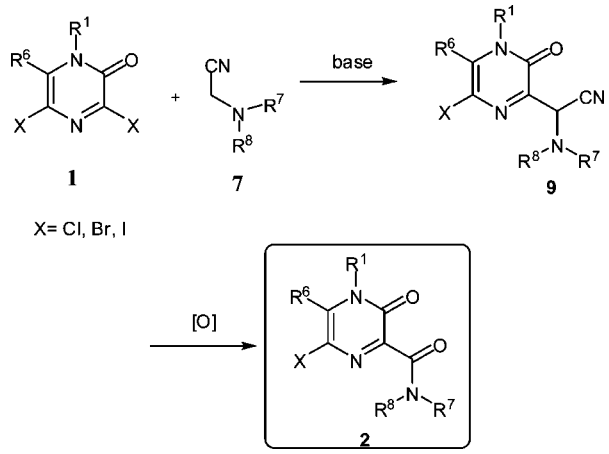
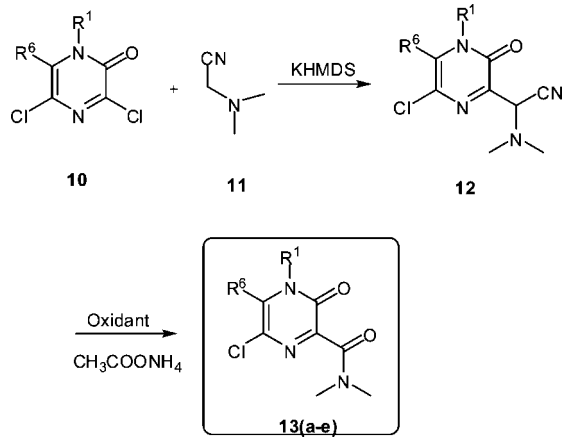


Table 1. Optimization of Oxidation Conditions



			(Yield %)		
	R^1	R^6	Na_2O_2	CH_3CO_3H	*m*-CPBA
13a	CH_2Ph	H	16	18	23
13b	CH_2CH_2Ph	H	13	18	28
13c	Ph	CH_3	23	24	27
13d	CH_2Ph	CH_3	27	32	32
13e	CH_2Ph	Ph(*p*-OMe)	34	33	49

To further optimize the reaction conditions, a stepwise analysis was performed. The generation of the intermediate **12** was achieved in 92% isolated yield which pointed out the problem to be in the oxidation step. Therefore three different oxidants were tried with five different pyrazinones **10a**−**e**, and the results are summarized in Table 1.

From this study, *m*-CPBA was found to be a higher yielding reagent than Na_2O_2 and CH_3CO_3H.

However, there are three limitations for this method. First, in this reaction different diaminoacetonitriles would be needed for the generation of different pyrazinone 3-carboxamides. Second, the amidoacetonitriles as amide synthons are restricted to N,N-disubstituted derivatives. The use of N-monosubstituted aminoacetonitriles would generate cyanoimine derivatives **16**, rather than primary amides (Figure 3).

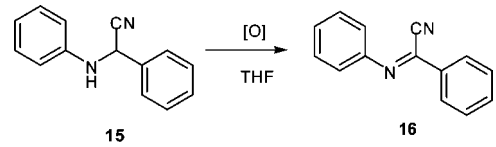


Figure 3. *N*-Monosubstituted aminoacetonitrile **15**, generating cyanoimine derivative **16**.

Finally, this method is low yielding. This would significantly restrict the generation of a diverse library of druglike compounds.

Therefore, in order to get widely substituted primary and secondary amide pyrazinones, the amino function of structure **7** must be replaced by a leaving group. Substituted acetonitriles **17** or **18** (Figure 4) could function in such way that

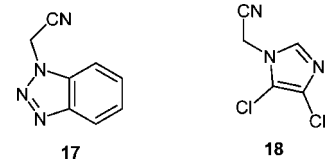


Figure 4. Substituted acetonitriles.

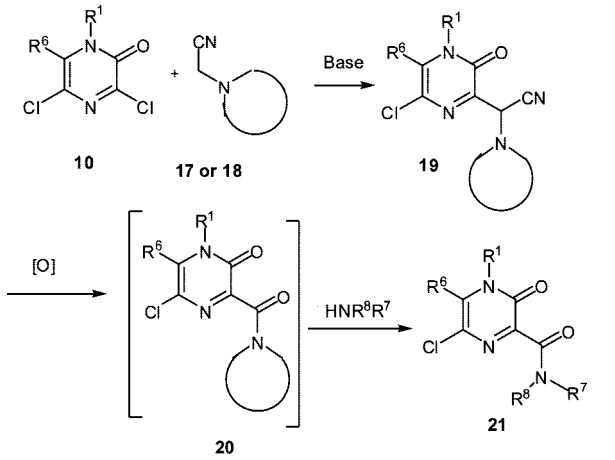
combination in the final step with any amine would give the corresponding amide. This approach could afford pyrazinone carboxamides **2** with differently substituted primary and secondary amides, directly from the corresponding dihalopyrazinones **1**.

It was anticipated that an anion generated from azole-*N*-acetonitrile **17** or **18** using a strong base would react with dichloro 2(1*H*) pyrazinone via S_NAr reaction to form the substituted aminoacetonitrile **19** (Scheme 4). The subsequent oxidation of **19** to the corresponding cyanohydrins would set the stage of elimination of HCN to afford an acylated azole derivative **20** that as an activated carbonyl derivative would react with an amine to provide the pyrazinone amide **21** (Scheme 4).

To a mixture of dichloro-2(1*H*)-pyrazinone **10a** (1 mmol) and imidazole *N*-acetonitrile (1.5 mmol) in dry THF was added KHMDS (2.5 mmol) at −78 °C. The reaction was complete within 5 h. The total conversion of dichloro 2(1*H*)-pyrazinone **10** to intermediate **19** was confirmed by LCMS. The intermediate **19** was then oxidized by subsequent addition of *m*-CPBA (4 mmol) and amine (3 mmol). The reaction mixture was stirred a further 10 h at room temperature, and the expected product **13a** was obtained in 60% yield (Table 2).[13]

(13) For experimental data, see the Supporting Information.

Scheme 4. Synthesis of Amides **21**



To generalize this one-pot process, a library of 12 pyrazinone 3-carboxamide derivatives was generated using six different dihalopyrazinones and eight different primary as well as secondary amines. The results are summarized in Table 2.

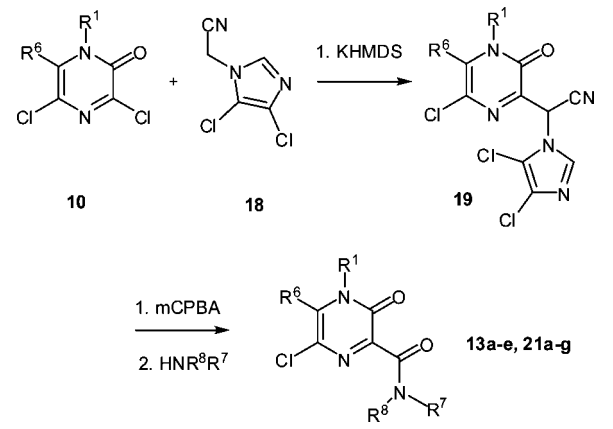
As shown in Table 2, this one-pot procedure affords products **13a**−**e** and **21a**−**g** in good overall yields.

This indicates the superiority of this method over the method using dimethylaminoacetonitrile. *m*-CPBA was found to be a good oxidizing reagent which gives a clean reaction compared to Na_2O_2 and CH_3CO_3H (entry **13a**).

In summary, novel and highly functionalized derivatives of pyrazinone carboxamide were synthesized in a single step starting from different dihalopyrazinones by taking advantage of its electrophilic C-3 position. Azole-*N*-acetonitriles derivatives as carbonyl synthon allow the introduction of a wide variety of primary and secondary amines. Thus highly functionalized pyrazinone scaffolds could be prepared, illustrating the wide scope of this scaffold as well as this mild and versatile method.

Acknowledgment. We thank the K.U. Leuven for financial support, including a doctoral fellowship for S.V.P. and a postdoctoral fellowship for V.G.P. The F.W.O.-Vlaanderen is thanked for a postdoctoral fellowship to W.M.D. and further project support.

Table 2. One-Pot Synthesis: Affording Primary and Secondary 3-Carboxamide Pyrazinone Derivatives **13** and **21**



	R^1	R^6	R^7	R^8	yield[a] (%)
13a	CH_2Ph	H	Me	Me	60[b],24[c],33[d]
13b	$(CH_2)_2Ph$	H	Me	Me	63[b]
13c	Ph	CH_3	Me	Me	74[b]
13d	CH_2Ph	CH_3	Me	Me	67[b]
13e	CH_2Ph	Ph (*p*-OMe)	Me	Me	83[b]
21a	CH_2Ph	Ph (*p*-OMe)	H	$(CH_2)_2CH(CH_3)_2$	73[b]
21b	CH_2Ph	Ph (*p*-OMe)	pyrrolidine		88[b]
21c	CH_2Ph	Ph (*p*-OMe)	Et	Et	72[b]
21d	CH_2Ph	Ph (*p*-OMe)	H	$(CH_2)_5CH_3$	81[b]
21e	CH_2Ph	Ph (p-OMe)	H	allyl	49[b]
21f	CH_2Ph	Ph (*p*-OMe)	H	CH_2Ph(*p*-OMe)	79[b]
21g	CH_2Ph	Ph (*p*-OMe)	H	$CH_2CH_2OCH_3$	76[b]

[a] Isolated yield using oxidant. [b] *m*CPBA. [c] Na_2O_2. [d] CH_3CO_3H.

Supporting Information Available: General experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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