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One-Step Continuous Flow Synthesis of Highly Substituted Pyrrole-3-carboxylic Acid Derivatives via in Situ Hydrolysis of *tert*-Butyl Esters

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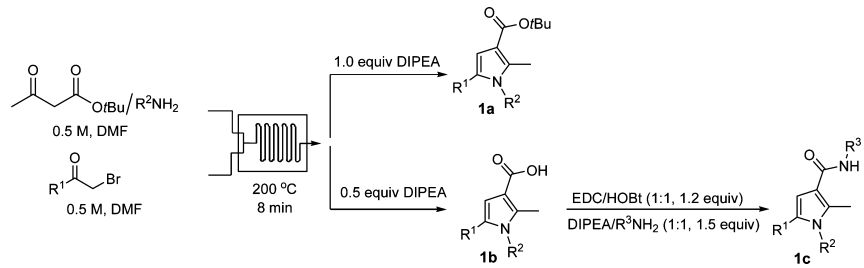
ABSTRACT



The first one-step, continuous flow synthesis of pyrrole-3-carboxylic acids directly from *tert*-butyl acetoacetates, amines, and 2-bromoketones is reported. The HBr generated as a byproduct in the Hantzsch reaction was utilized in the flow method to hydrolyze the *t*-butyl esters in situ to provide the corresponding acids in a single microreactor. The protocol was used in the multistep synthesis of pyrrole-3-carboxamides, including two CB1 inverse agonists, directly from commercially available starting materials in a single continuous process.

Automated microreactor-based (microfluidic chip) continuous flow chemistry is emerging as a powerful technology for the synthesis of small molecule compounds.[1a,b] The application of continuous flow methods to the production of libraries of druglike structures (primarily heterocycles) has the potential to greatly accelerate the drug discovery process.[1c] Continuous flow synthetic methods have the advantage of being highly efficient, atom economical,[2a,b] environmentally friendly (reduction of waste streams), and cost-effective.[2a−f] Moreover, the potential to run multistep reactions in a single, uninterrupted microreactor sequence using continuous flow chemistry is particularly beneficial for the rapid and efficient generation of large numbers of compounds with high purity and minimal byproducts.[2c−h] Our research is focused on developing flow chemistry methods for multistep transformations that are either not possible or highly inefficient using in-flask chemistry. We have previously reported general methods for the preparation of 1,2,4-oxadiazoles and imidazo[1,2-a]pyridine-2-carboxamides in uninterrupted continuous flow sequences.[2c,d] We now report an efficient continuous flow procedure for the synthesis of functionalized,

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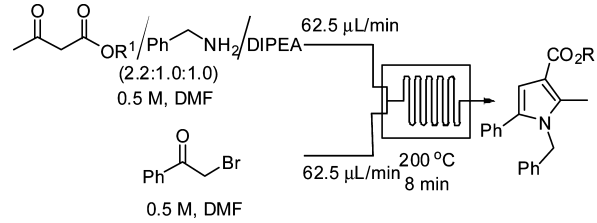
highly diverse derivatives of the pyrrole-3-carboxylic acid scaffold.

The pyrrole framework is a ubiquitous structural motif found in a wide range of biologically active natural products and pharmaceutically active agents.[3] Members of this important class of heterocyclic compounds display a variety of pharmacological properties including antibacterial, antiviral, anti-inflammatory, anticancer, and antioxidant activity.[4] A prime example is atorvastatin calcium (Lipitor), the world's leading cholesterol-lowering drug.[5] Consequently, there is significant interest in the development of efficient methods for the synthesis of pyrrole derivatives bearing diverse substitution patterns. There are several classical methods for the synthesis of pyrroles, including the Hantzsch,[6] Paal−Knorr,[7] and Knorr, in addition to a variety of cycloadditions[8] and transition-metal-catalyzed cyclization reactions.[9] Although these methods have proven effective for the preparation of pyrrole derivatives, they involve multistep in-flask (batch) syntheses that limit scope and efficiency, especially with respect to analogue library synthesis.

The Hantzsch pyrrole synthesis involves the reaction of β-ketoesters with ammonia (or primary amines) and α-haloketones.[6a] Although the Hantzsch method produces N-substituted pyrroles, the yields are often low, and this may be why the procedure has been somewhat under utilized historically.[6c,10a] Furthermore, the "one-pot" synthesis of pyrrole-3-carboxylic acids has not been reported, and thus stepwise, in-flask (batch) protocols are necessary.[10b] Herein, we describe the first direct continuous flow synthesis of pyrrole-3-carboxylic acids. In addition, we have applied the method to the synthesis of pyrrole-3-carboxamide derivatives in an uninterrupted sequence.

Our investigations initially focused on the direct synthesis of pyrroles from commercially available ethyl acetoacetate (2.2 equiv), benzylamine (1.0 equiv), and α-bromoacetophenone (1.0 equiv). A variety of bases such as *N*,*N*-diisopropylethylamine (DIPEA), triethylamine, 2,6-lutidine, pyridine, and 2,6-di-*tert*-butylpyridine were screened at different temperatures using a single microreactor. It was found that the use of DIPEA (1.0 equiv) in dimethylformamide (DMF) at 200 °C was most efficient for this process. A solution of ethyl acetoacetate/benzylamine/DIPEA (2.2:1:1, 0.5 M, DMF) and α-bromoacetophenone (1.0 equiv, 0.5 M, DMF) was introduced into a preheated microreactor at 200 °C and 5.0 bar (Table 1). Analysis of the reactions by LC−MS showed that the conversion of α-bromoacetophenone to the corresponding pyrrole derivatives was complete within 8 min. This reaction tolerated a variety of β-ketoesters including ethyl, benzyl, methyl, and *tert*-butyl acetoacetates (Table 1).

Table 1. Scope of β-Ketoesters



entry	R^1	yield (%)[a]
1	Me	82
2	Et	81
3	Bn	78
4	*t*Bu	76

[a] Isolated yield based on benzylamine after purification of the crude reaction mixture.

tert-Butyl esters are versatile protecting groups for carboxylic acids which are stable under basic conditions but can be removed using acid.[11] Typically strong protic acids, such as HCl, H_2SO_4, HNO_3, or TFA, are employed for *tert*-butyl ester hydrolysis in aqueous or organic solvents.[12] During the Hantzsch pyrrole synthesis, HBr is generated as a side product, and in our procedure DIPEA is used as a neutralizing agent. We hypothesized that we could take advantage of the strong acid generated in the Hantzsch reaction to hydrolyze the *tert*-butyl ester formed in the initial product. With this in mind, we varied the reaction conditions

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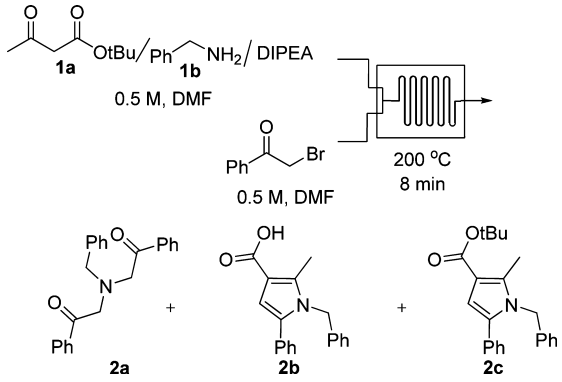
using different equivalents of DIPEA (Table 2) and found that the use of 0.5 equiv of DIPEA was optimal to efficiently

Table 2. Optimization of the Synthesis of Pyrrole-3-carboxylic Acids



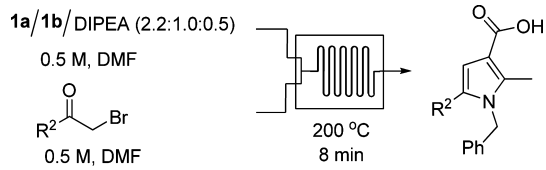
entry	**1a**:**1b**:**DIPEA**	products **2a**:**2b**:**2c**[a]
1	3:1:0.25	44:56[b]
2	3:1:0.5	14:75:11
3	3:1:0.6	15:68:17
4	3:1:0.7	14:62:24
5	3:1:0.8	13:47:40
6	3:1:0.9	10:10:80
7	3:1:1	4:2:94

[a] Compound ratios were determined using LC−MS. [b] Compound **2c** was not observed.

convert the *tert*-butyl ester pyrroles to the corresponding acids in situ (Table 2, entry 2).

A variety of substrates were amenable to the reaction conditions, and good to high yields of the corresponding pyrrole-3-acids were obtained (Table 3). Reactions of α-bromoacetophenones having electron-donating (Table 3, entries 1 and 6) or electron-withdrawing groups (Table 3, entries 3−5) proceeded efficiently with moderate to good yields. The product in Table 3, entry 8, is notable since it is a dicarboxylic acid that is monoprotected as the ester, allowing selective functionalization of the free acid in subsequent synthetic transformations. Additionally, the reaction can tolerate a variety of primary amines such as allyl, cyclic, linear, and branched alkylamines to provide N-substituted pyrroles (Table 4). One intriguing

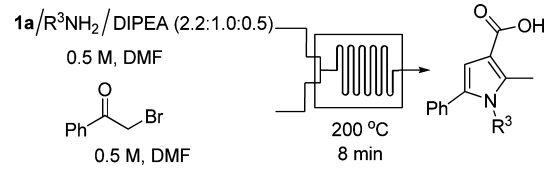
Table 3. Scope of α-Bromoketones

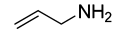
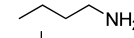
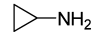
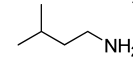
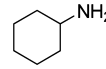
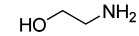


entry	R^2	yield (%)[a]
1	Ph	65
2	4-$OMeC_6H_4$	61
3	4-FC_6H_4	60
4	4-CNC_6H_4	48
5	4-$NO_2C_6H_4$	61
6	3-OHC_6H_4	57
7	4-BrC_6H_4	64
8	CO_2Et	40

[a] Isolated yield based on **1b** after purification of the crude reaction mixture.

Table 4. Scope of Amines



entry	R^3NH_2	yield (%)	entry	R^3NH_2	yield (%)[a]
1		62	4		59
2		61	5		54
3		58	6		40

[a] Isolated yield based on amine after purification of the crude reaction mixture.

observation was that this new method can be employed to generate free hydroxyl group-containing pyrrole carboxylic acids in an efficient manner, without the use of a protecting group (Table 4, entry 6).

We were also able to extend the methodology to the synthesis of N−H pyrrole acids. Thus, the required starting material, *tert*-butyl 3-aminobut-2-enoate, was obtained by simply mixing 3 equiv of ammonium carbamate (NH_4OOCNH_2) and *tert*-butylacetoactate in methanol for 15 min.[13] As shown in Table 5, the preparation of N-unsubstituted pyrrole-3-acids proceeds in uniformly good yields. To demonstrate the utility of the newly developed methodology, our next goal was to develop a continuous flow method to access pyrrole-3-carboxamides in a single, uninterrupted process directly from readily available starting materials.

Previously, we demonstrated that the conversion of heterocyclic acids to amides was efficient using a solution of EDC/HOBt and amine/DIPEA in a second microreactor at 75 °C for 10 min.[2c] However, the use of the same conditions provided a low conversion of pyrrole-3-carboxylic acids to the corresponding amides. Several attempts were made to generate amides using a second microfluidic chip.

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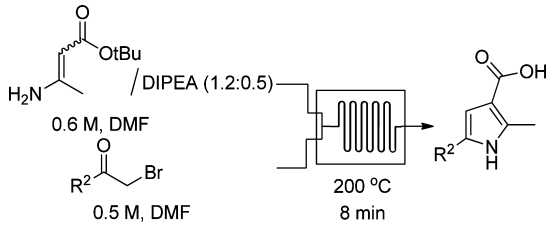
Table 5. Synthesis of 1*H*-Pyrrole-3-carboxylic Acids

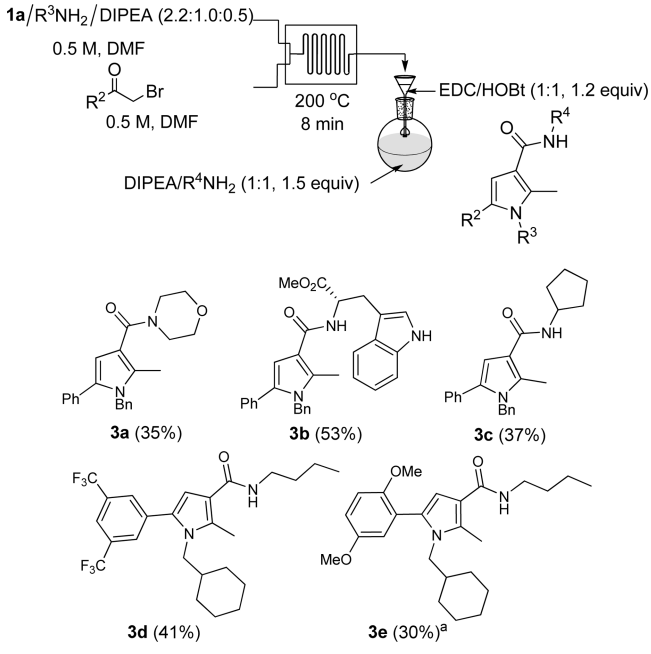


entry	R^2	yield (%)[a]
1	Ph	60
2	4-$OMeC_6H_4$	60
3	4-FC_6H_4	62
4	4-CNC_6H_4	48

[a] Isolated yield based on α-bromoketone after purification of the crude reaction mixture.

All flow reaction conditions attempted led to low conversion to product. To overcome this obstacle, the stream containing the pyrrole-3-carboxylic acid exiting the first microreactor was combined first with EDC/HOBt (1:1, 1.2 equiv) and then with amine/DIPEA (1:1, 1.5 equiv) in a collecting vial and stirred overnight at room temperature (Scheme 1). This process tolerates a range of amines including primary (Scheme 1, **3c**−**3e**) and secondary (Scheme 1, **3a**). Additionally, amino acid derivatives can directly couple efficiently to introduce further complexity to the final compounds (Scheme 1, **3b**).

Scheme 1. Direct Synthesis of Pyrrole-3-carboxamides



[a] 0.25 equiv of DIPEA was used.

Finally, to demonstrate the utility of the new method we synthesized compounds **3d** and **3e** which were recently disclosed as cannabinoid receptor subtype 1 (CB1R) inverse agonists.[14a,b] There is significant interest in small molecule CB1R inverse agonists within the pharmaceutical sector because of their potential to treat various CNS disorders including obesity and drug dependence.[14c] The reported in-flask synthesis of **3d** and **3e** required three separate steps, while the same compounds were prepared very efficiently using our flow method in a single step (Scheme 1).

Several aspects of this new continuous flow process are noteworthy. For example, this is the first instance of the synthesis of pyrrole-3-carboxylic acids and pyrrole-3-carboxamides directly from inexpensive commercially available starting materials in a single continuous process without isolating intermediates. As noted previously, the standard in-flask synthesis of these compounds involves multiple reaction steps requiring workup and purification of several intermediates. Second, the HBr generated as a byproduct in the Hantzsch reaction is employed in the flow method to hydrolyze the *t*-butyl esters in situ to provide the corresponding acids in a one-chip reaction. By way of comparison, we performed the in-flask (batch) synthesis of 1-benzyl-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid (Table 3, entry 1) using the optimized conditions we developed for our continuous flow method (see Supporting Information for experimental details). Interestingly, the reaction proceeded as expected to provide the product but in significantly lower yield (40%) than the flow process (65%). Finally, the products can be further manipulated in the final step by coupling diverse amines to generate a variety of amides allowing the introduction of additional structural complexity. To demonstrate the utility of the flow method to generate useful quantities of material for further synthetic manipulation, we scaled up the flow synthesis of 1-benzyl-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylic acid (Table 3, entry 1) by approximately 17-fold. Gratifyingly, using the flow method, 850 mg (63% yield) of the compound was efficiently produced in 2.5 h flow time.

In summary, we have developed the first general method for the synthesis of diversely substituted pyrrole-3-carboxylic acids and amides directly from commercial *tert*-butyl acetoacetates, amines, and α-bromoketones. We anticipate that these advances will facilitate the rapid synthesis of these biologically important compounds. Further exploration of the reactivity features of this methodology and applications to the synthesis of complex molecules and the drug discovery process are in progress.

Acknowledgment. This work was supported by National Institutes of Health grant nos. HG005033, GM079590, and GM081261.

Supporting Information Available: Experimental procedures and characterization data for all compounds including ^1H and ^{13}C NMR spectra and MS data. This material is available free of charge via the Internet at http://pubs.acs.org.

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