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Synthesis of Fused Indolines by Interrupted Fischer Indolization in a Microfluidic Reactor

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Abstract

This study describes our development of a microfluidic reaction scheme for the synthesis of fused indoline ring systems found in several bioactive compounds. We have utilized a continuous-flow microfluidic reactor for the reaction of hydrazines with latent aldehydes through the interrupted Fischer indolization reaction to form fused indoline and azaindoline products. We have identified optimal conditions and evaluated the scope of this microfluidic reaction using various hydrazine and latent aldehyde surrogates. This green chemistry approach can be of general utility to rapidly produce indoline scaffolds and intermediates in a continuous manner.

Graphical Abstract

Keywords

Flow chemistry; Interrupted Fischer Indolization; Microfluidic reactor; (Aza)indoline; Latent aldehyde

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ASSOCIATED CONTENT

Supplementary Data

Supplementary data (¹H and ¹³C NMR spectra for all new compounds) associated with this article can be found, in the online version, at <http://dx.doi.org/>

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Introduction

The discovery and development of efficient methods using microfluidic flow chemistry to rapidly synthesize bioactive molecules is of great value for hit-to-lead optimization efforts.^{1–3} However, microfluidic transformations of basic reactions are still limited due to engineering feasibility for translating heterogeneous reactions in a flow reactor.^{4–8} A vast majority of low molecular weight bioactive molecules are heterocyclic, and often comprised of several connected heterocyclic rings.^{9–11} A small subset of molecules that have received substantial interest due to their medicinal properties are furoindoline and pyrrolidinoindoline that possess a fused indoline motif as shown in Figure 1. These scaffolds are present in many naturally occurring alkaloids.^{12–19}

The Fischer indolization reaction is an efficient way to construct fused indoline ring-systems, although several alternate methods have also been developed to access these biologically important motifs.^{19,20} A variant of this reaction, the Garg interrupted Fischer indolization, has the advantage of producing three new bonds, two heterocyclic rings and two stereogenic centers, in one reaction.^{15,16} This methodology is convergent, broad in scope, proceeds under mild reaction conditions, and can be used to synthesize a variety of natural products.¹⁵ In one such example this transformation has been recently utilized in the total synthesis of Aspidophylline A (**3**) and its aza analog.^{18,22}

Continuous-flow microfluidic reactor based approaches allow for rapid synthesis of products in a green chemistry mode.² While there are few reports on Fischer indolization reactions using a microfluidic reactor, this is not the case with the interrupted Fischer indolization reaction to the best of our knowledge.^{23–25} We describe here the development of a microfluidic reactor process for the preparation of indoline and azaindoline compounds using the interrupted Fischer indolization reaction, which complements known batch chemistry (Scheme 1).¹⁵ This microfluidic reaction allows for the synthesis of indoline-containing products by the reaction of hydrazines and latent aldehydes under mildly acidic conditions. The methodology allows for efficient reagent mixing, smaller reaction volumes, optimal heat transfer, precise reaction (retention) times, and the possibility to conduct multistep reactions in a single or continuous sequence. Thus, this microfluidic approach can be of general utility for synthesis of such biologically relevant molecules in a safe, environmentally friendly, and cost effective manner that could be amenable to large scale manufacturing.

Results and discussion

Our approach to obtain indoline scaffolds in the microfluidic reactor using the interrupted Fischer indole synthesis is shown in the scheme 1.¹⁵ As part of developing this transformation we initially tried the reaction of phenyl-hydrazine (**4**) and lactol (latent aldehyde) **5** in the reactor using (1:1) AcOH:H₂O at 60 °C and 1 bar pressure to determine if we could obtain furoindoline **6**. Unfortunately, we did not get any product under these conditions. Next we changed the temperature, pressure and retention time in the microfluidic reactor to determine the reaction outcome. Next we systematically change temperature, pressure, and retention time in the microfluidic reactor to determine the reaction outcome.

After several variations we found that successful interrupted Fischer indolization reaction occurred at 80 °C, 2 bar pressure, and 20 min retention time in the microfluidic reactor affording the desired furoindoline **6** in 84% yield (entry 5). Further increasing the temperature, pressure and retention time in the microfluidic reactor led to the optimal conditions of 120 °C, 3 bar pressure and 5 min retention time in the microfluidic reactor affording a 97% yield of **6** as determined by HPLC (entry 8). Scale up and purification gave 285 mg of furoindoline **6** in 65% isolated yield (details in supplementary information).

After identifying the optimal microfluidic conditions for the interrupted Fischer indolization, we next conducted the reaction using different hydrazines while keeping the latent aldehyde (**5**) constant. As shown in Table 2, the reaction is broad in scope with respect to the hydrazine surrogates. Both para- and ortho- substituents were tolerated under the microfluidic reaction condition (entries 1, 2, 4, 5 and 6) and afforded the corresponding furoindoline products in good yields. The *N*-methyl-substituted hydrazine **9** was shown to be a competent coupling partner (entry 3) and afforded the desired *N*-methyl furoindoline **16** in 68% yield while use of the *p*-methoxypyridylhydrazine salt **13** afforded the furanoazaindoline **20** in moderate 40% yield (entry 7). Several of the products such as the haloindolines (entries 2, 5, 6), are setup for further functionalization by transition-metal-catalyzed cross-coupling chemistry.

We further evaluated the scope of the transformation with nitrogen- or oxygen-containing latent aldehyde coupling partners using phenyl hydrazine **4** (Table 3). The use of five-membered oxygen- or nitrogen-containing latent aldehydes, under more dilute conditions for solubility, afforded the corresponding furoindoline **24** and pyrrolidinoindoline **25** in 49% and 42% yield, respectively. Interestingly, even the six-membered homolog (**26**) of the pyrrolidinoindoline framework was obtained using this methodology, although in lower yield.

Conclusion

The use of a microfluidic reactor for the interrupted Fischer indolization resulted in short reaction times and led to indoline and azaindoline products in reasonable yields. We were able to accelerate the microfluidic reaction by increasing temperature and pressure to achieve yields upto 97% with 5 minutes residence time in the reactor. This rapid green chemistry methodology should facilitate continuous synthesis of fused indoline ring systems that can potentially be coupled with additional microfluidic reactors for multistep synthesis. This approach allows for rapid synthesis of these important scaffolds as dual enzyme inhibitors and should prove useful for the discovery of new drug candidates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights:

- Development of microfluidic reaction scheme for synthesis of fused indoline ring systems by flow chemistry
- Green chemistry approach with clean reaction profile, good yields and quick scalability.
- Continuous-flow in a microfluidic reactor for interrupted Fischer indolization reaction.
- General utility to rapidly produce indoline scaffolds and intermediates of industrial importance

(-)-Phenserine (phenserine) (1)
Inhibitor of acetylcholinesterase

Madindoline A (2)
Selective inhibitor of Interleukin 6

Aspidophylline A (3)
Reverse drug resistance in resistant KB cells

Figure 1.
Example of representative bioactive compounds containing fused indolines.

Synthetic Scheme 1.

Table 1.

Optimization of interrupted Fischer indolization in a microfluidic reactor^a

Entry	Pressure (bar)	Temperature (°C)	Flow Rate ^b (μL/min)	Retention Time ^c (min)	Yield ^d (%)
1 ^e	1	60	500	2	0
2 ^e	2	70	500	2	0
3 ^e	2	70	200	5	0
4 ^e	2	80	200	5	0
5 ^e	2	80	50	20	84
6 ^e	2	100	50	20	97
7 ^f	3	120	100	10	97
8 ^f	3	120	200	5	97 ^g

^aSynthesis of compound **6** was done under varying conditions (entry 1 – 8); two solutions were prepared and introduced by Pump A & B into the Asia microfluidic reactor; one contained the phenyl hydrazine **4** (1.0 equivalent) in AcOH–H₂O (2.5 mL, 1:1 v/v) and the other contained latent aldehyde **5** (1.1 equivalent) in AcOH–H₂O (2.5 mL, 1:1 v/v).

^bCombined flow rate from both pumps.

^cResidence time in microfluidic chip reactor (1000 μL volume).

^dHPLC yield from microfluidic flow reactor.

^eHydrazine added at 0.2 M. Latent aldehyde at 1.1 equiv.

^fHydrazine added at 0.5 M. Latent aldehyde at 1.1 equiv.

^gScale-up of reaction yielded furoindoline **6** in 65% yield.

Table 2.

Hydrazine variants in the microfluidic interrupted Fischer indolization reaction^a

Entry	Hydrazine Variant	Product	Yield
1	7	14	78%
2	8	15	57%
3	9	16	68%
4	10	17	34%
5	11	18	55%

Entry	Hydrazine Variant	Product	Yield
6			56%
7			40%

^aThe reactions were performed using optimized condition (see Table 1, entry 8); two solutions were prepared and introduced by Pump A & B into the Asia microfluidic reactor; one contained the different hydrazine surrogates (**7–13**) (1.0 equivalent) in AcOH–H₂O (2.5 mL, 1:1 v/v) and the other contained latent aldehyde **5** (1.1 equivalent) in AcOH–H₂O (2.5 mL, 1:1 v/v). Average isolated yields from at least two trials for products (**14–20**) are reported.

Table 3.

Variations of the latent aldehyde surrogate in the microfluidic reaction ^a

Entry	Lactol Variant	Product	Yield
1 ^b	<p>21</p>	<p>24</p>	49%
2 ^c	<p>22</p>	<p>25</p>	42%
3 ^d	<p>23</p>	<p>26</p>	21%

^aThe reactions were performed using optimized conditions (see Table 1, entry 8); two solutions were prepared and introduced by Pump A & B into the Asia microfluidic reactor; one contained the phenyl hydrazine (**4**) (1.0 equivalent) in AcOH–H₂O (0.5 mL, 1:1 v/v) and the other contained lactol variant (**21–23**) (1.1 equivalent) in AcOH–H₂O or AcOH (0.5 mL, 1:1 v/v). Average isolated yields from at least two trials for products (**24–26**) are reported.

^bHydrazine added at 0.4 M. Latent aldehyde at 1.1 equivalent due to insolubility of latent aldehyde **21**.

^cHydrazine added at 0.1 M. Latent aldehyde at 1.1 equivalent due to insolubility of latent aldehyde **22**.

^dHydrazine added at 0.4 M. Latent aldehyde at 1.1 equivalent due to insolubility of latent aldehyde **23** & reaction performed in AcOH.