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## **Harnessing interrupted Fischer in continuous flow: sustainable synthesis of (spiro)indolenine and (spiro)indoline privileged scaffolds**

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## **Abstract**

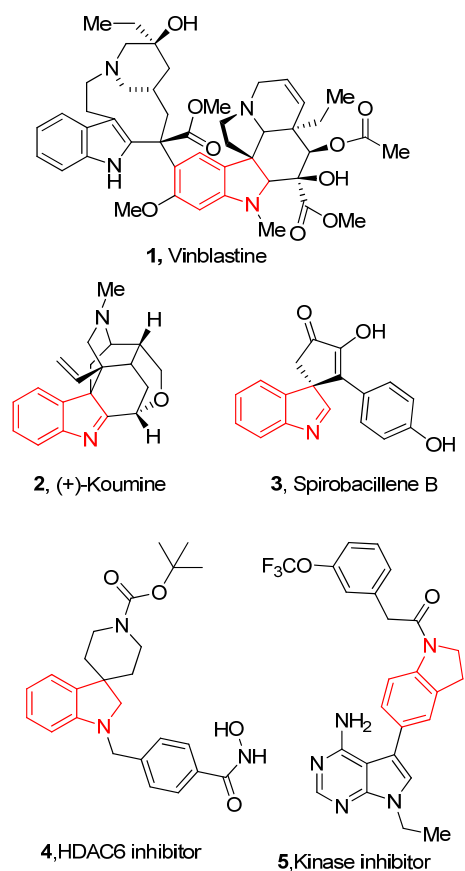
A greener and sustainable flow chemistry protocol for the synthesis of 3,3-disubstituted indolenines through interrupted Fischer indolisation reaction is described. First, two model aldehydes were reacted with phenylhydrazine in order to explore the reaction feasibility in a 'greener' fashion in batch mode. The best outcomes were then used as the starting point for the implementation of the reaction in continuous flow. A thorough exploration of key parameters allowed the identification of the most efficient reagent mixing mode, and the optimum temperature and residence time. The newly developed method allowed straightforward reaction channelling towards the formation of the indolenines, thus reducing the competitive formation of side products. We further broadened the scope of the conceived methodology by exploring the possibility of a heterogeneous in-line reduction of the indolenines to their indoline counterparts. The rapid approach nicely complements known batch chemistry and could facilitate synthesis and scale up of 3,3-disubstituted indolenines and indolines, offering a coupling point for additional and subsequent flow reactions for multistep syntheses for further derivatization.

## **Keywords**

indolines; flow-chemistry; interrupted Fischer; sustainable synthesis; privileged scaffolds

## Introduction

Nitrogen-containing heterocycles display crucial importance in medicinal chemistry and drug design, as demonstrated by their striking predominance in marketed drugs.<sup>1</sup> Owing to their wide variety of biological activities, indole- and indoline-based structures have always deserved special importance as privileged scaffolds, being broadly found in medicinally relevant compounds of natural and synthetic origins (**Figure 1**, compounds **1-5**).<sup>2-5</sup> Numerous alkaloids possess the indoline or spirocyclic indoline motif and this significantly fostered synthetic research efforts towards the achievement of indoline-based complex molecules as well as simpler architectures for medicinal chemistry application.<sup>6-9</sup>



**Fig. 1.** Structures of indoline- and indolenine-containing alkaloids (**1-3**) and synthetic medicinally relevant compounds **4** and **5**.

A broad array of protocols for the synthesis of 3,3-disubstituted indolenines and their indoline counterparts have been reported over years, which can be clustered into three main categories: i) interrupted Fischer indolisations,<sup>10, 11</sup> ii) dearomatisation of indole derivatives,<sup>12, 13</sup> and iii) condensation reactions.<sup>14</sup> Owing to their versatile reactivity, indolenines can further function as useful precursors for other privileged heterocycles, including oxindoles, carbazoles, and indoles (**Figure 2**, paths I-III).<sup>15, 16</sup> Moreover, highly diverse cyclic Schiff bases can be generated by an interrupted Fischer between  $\alpha,\alpha'$ -disubstituted carbaldehydes and (hetero)aromatic hydrazines under acidic conditions. This is a highly versatile synthetic transformation *per se*, since Schiff bases are key intermediates of the majority of isocyanide-based multicomponent reactions (**Figure 2**, path IV).<sup>17-19</sup>

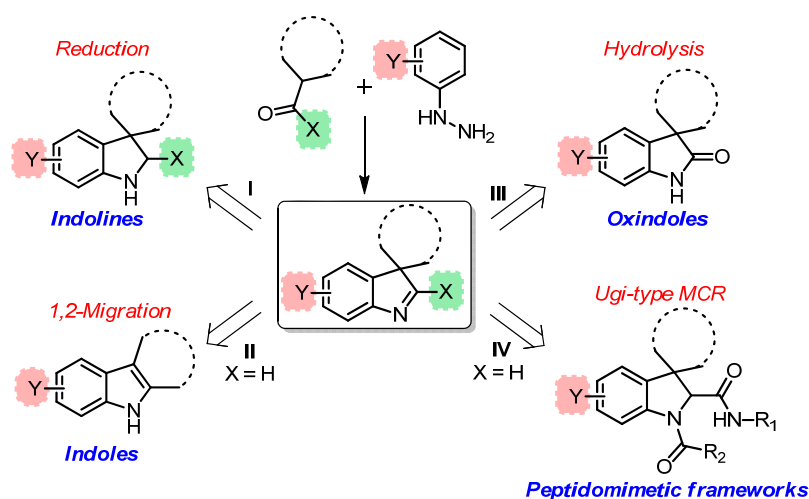
We herein disclose the implementation of a continuous flow protocol for the synthesis of 3,3-disubstituted indolenines using a sustainable interrupted Fischer indolisation. A first investigation in batch carried out on model  $\alpha,\alpha'$ -disubstituted carbaldehydes allowed to set up the starting point for the implementation of the reaction in segmented continuous flow mode, as we were ultimately aiming at developing a way for rapid scaffold derivatization within screening efforts.<sup>20-24</sup> We hence aimed at a protocol of general utility for the synthesis of 3,3-disubstituted indolenines in a safe, environmentally friendly, and cost-effective mode that additionally could be amenable to larger scale manufacturing. We further broadened the scope of the conceived methodology by exploring the possibility of an in-line reduction of the indolenines to their indoline counterparts, also in a telescoped manner such to provide starting solutions of indolines for further reactions. The number of examples and the variability of the nature of aldehydes and phenylhydrazines successfully converted, witness the broad scope and utility of the proposed methodology.

## Results and discussion

### *Basic screening of reaction conditions in batch*

Although representing a useful and versatile structural template and a privileged scaffold for medicinal chemistry, the 3,3'-disubstituted indolenine framework is associated with significant challenges which should be taken into account when designing synthetic protocols for their preparation. First, the propensity of the metastable indolenines to undergo 1,2-migration under acidic conditions towards the more thermodynamically stable indole counterparts imposes the need for fast removal of the acidic catalysts from the reaction medium and/or rapid conversion into more stable derivatives.<sup>25-27</sup> Moreover, as observed for other imine substrates, 3,3'-disubstituted indolenines are found in equilibrium with their imine trimer form, which, however, should easily collapse in situ.<sup>15</sup>

The interrupted Fischer indolisation represents the oldest reported synthesis of a 3,3'-disubstituted indolenines.<sup>27</sup> Implementation of the Fischer indole synthesis in flow has attracted significant attention in the past few years, since general reaction conditions are highly adaptable to continuous-flow techniques.<sup>28-32</sup> Moreover, continuous flow-based approaches also allow for rapid synthesis of products in screening efforts, eventually also in a green chemistry fashion.<sup>33</sup> Despite several reports on Fisher indole synthesis using continuous flow conditions, only sporadic investigation has been performed on its interrupted variation.<sup>34</sup> We herein propose a green version of an interrupted Fischer indolisation reaction in continuous flow employing a sustainable protocol for the preparation of 3,3-disubstituted indolenines.



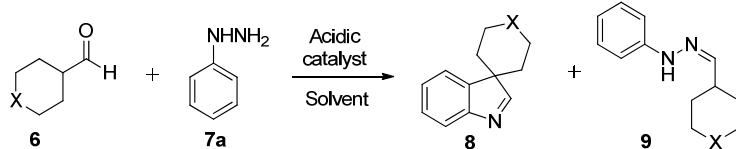
**Fig. 2.** Utility of 3,3-disubstituted indolenines as precursors for other privileged heterocycles and substrates for multicomponent reactions.

As a preliminary task, in our quest to shift towards a ‘greener’ and sustainable protocol for the synthesis of 3,3-disubstituted indolenines/indolines, we decided to examine the behavior of two aldehydes, namely 1-Boc-piperidine-4-carboxaldehyde and cyclohexylaldehyde as model compounds in batch reaction conditions. These two model aldehydes were chosen due to the following reasons: i) being both  $\alpha,\alpha'$ -disubstituted cyclic aldehydes, they would provide spirocyclic indolenines which are generally more prone to undergo the above-described 1,2-migration path; a good outcome for an interrupted Fischer protocol on these substrates would easily guarantee an even better performance on more tractable  $\alpha,\alpha'$ -disubstituted acyclic aldehydes; ii) *N*-Boc functionality, despite being and in ideal protecting group for amines, is an acid-labile chemical functionality; its stability under the employed Fischer reaction conditions would guarantee the construction of spiroindoline-based substructures with a useful handle for subsequent selective functionalization of both nitrogen atoms of the spiroindoline privileged scaffold.

As summarized in Table 1, starting from classical reaction conditions employing acetic acid with the dual role of solvent and acidic catalyst for Fischer indole synthesis (Table 1, entry 1), we embarked a systematic exploration of solvents, acidic catalysts and reaction temperature and time. The attempts on an equimolar mixture of 1-Boc-piperidine-4-carboxaldehyde and phenylhydrazine (free base) employing

isopropanol as benign and sustainable solvent option and acetic acid (Table 1, entry 2) or Amberlyst 15 (Table 1, entry 3) as the catalyst, suggested as options in the archival literature for similar cyclisation problems,<sup>31, 35</sup> did not provide the desired product. In particular, when using Amberlyst 15 as the catalyst, only the phenylhydrazone precursor **9** could be detected in 85% by GC analysis. We also obtained rather disappointing outcomes when using ethyl acetate as the green solvent system, coupled with either Amberlyst 15 or *p*-toluenesulfonic acid as the catalysts (Table 1, entries 4 and 5, respectively). Both methods led to the formation of the phenylhydrazone byproduct, although to different extent, with only a minor percentage of the spiroindolenine product **8** detected in the reaction catalysed by *p*-toluenesulfonic acid. The first reversion of this trend was achieved when employing phenylhydrazine as its hydrochloride salt, as the *in situ* source of one equivalent of hydrochloric acid, and ethanol as the solvent at 50° C (Table 1, entry 6). The desired product was obtained in 45% yield, while its phenylhydrazone counterpart was formed in 32% yield. A comparable behavior was observed using the cyclohexylcarboxaldehyde and phenylhydrazine as the free base (Table 1, entries 7-11), with only small amounts of compounds formed in case ethanol was used as solvent and Amberlyst 15 or *p*-toluenesulfonic acid as catalysts (Table 1, entries 9 and 11, respectively). Gratifyingly, the use of phenylhydrazine hydrochloride in ethanol at 50° C for 2 hours provided the best outcome, with a 90% yield and no trace of the phenylhydrazone.

**Table 1** Optimization of reaction conditions in batch for the preparation of 3,3-disubstituted indolenines.



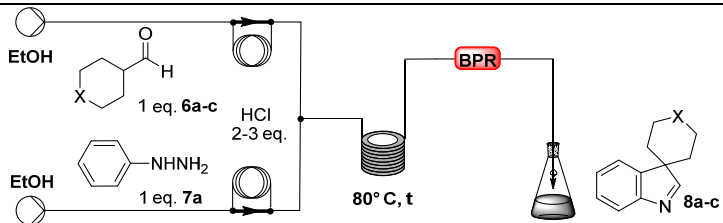
| Entry <sup>[a]</sup> | X                             | Aldehyde (mmol) | PhNHNH <sub>2</sub> (mmol) | Acid (equiv.)  | Solvent | Temp (°C) | Time (h) | Yield <b>8</b> (%) <sup>[a]</sup> | Yield <b>9</b> (%) <sup>[b]</sup> |
|----------------------|-------------------------------|-----------------|----------------------------|----------------|---------|-----------|----------|-----------------------------------|-----------------------------------|
| 1                    | N-Boc ( <b>6a</b> )           | 0.5             | (free base)                | AcOH           | AcOH    | 80        | 2        | 73                                | n.d.                              |
| 2                    |                               | 0.5             | (free base)                | AcOH           | iPrOH   | 80        | 12       | n.d.                              | n.d.                              |
| 3                    |                               | 0.5             | (free base)                | Amberlyst 15   | iPrOH   | 80        | 12       | n.d.                              | 85                                |
| 4                    |                               | 0.5             | (free base)                | Amberlyst 15   | EtOAc   | 25        | 12       | n.d.                              | 21                                |
| 5                    |                               | 0.5             | (free base)                | <i>p</i> -TsOH | EtOAc   | 80        | 12       | 23 <sup>[b]</sup>                 | 67                                |
| 6                    |                               | 0.5             | (HCl salt)                 | -              | EtOH    | 50        | 4        | 45 <sup>[b]</sup>                 | 32                                |
| <hr/>                |                               |                 |                            |                |         |           |          |                                   |                                   |
| 7                    | CH <sub>2</sub> ( <b>6b</b> ) | 0.5             | (free base)                | AcOH           | AcOH    | 80        | 2        | 85                                | n.d.                              |
| 8                    |                               | 0.5             | (free base)                | AcOH           | AcOH    | 50        | 2        | n.d.                              | n.d.                              |
| 9                    |                               | 0.5             | (free base)                | Amberlyst 15   | EtOH    | 80        | 4        | 16 <sup>[b]</sup>                 | n.d.                              |
| 10                   |                               | 0.5             | (free base)                | Amberlyst 15   | EtOH    | 50        | 2        | n.d.                              | n.d.                              |
| 11                   |                               | 0.5             | (free base)                | <i>p</i> -TsOH | EtOH    | 50        | 4        | 13 <sup>[b]</sup>                 | 53                                |
| 12                   |                               | 0.5             | (HCl salt)                 | -              | EtOH    | 50        | 2        | 90 <sup>[b]</sup>                 | n.d.                              |
| 13                   |                               | 0.5             | (HCl salt)                 | Amberlyst 15   | EtOH    | 50        | 2        | 80 <sup>[b]</sup>                 | n.d.                              |

[a] Isolated yields; n.d.: not determined. [b] Conversion ratio as determined by standardized GC-MS analysis.

### *Development of reactions conditions in segmented continuous flow mode*

Based on these initial results, reliable flow conditions were elaborated. Following the idea that flow chemistry applications do not need prefabricated flow systems, our flow system was realized in a comparably cost-effective fashion: two conventional HPLC pumps were connected to two six-port Rheodyne injectors for meso-scale preparative HPLCs, that were equipped each with 2 mL volume sample loops made from PTFE tubing and an injection port for conventional disposable syringes. Connection to the 15 mL volume tubular reactor made from PTFE tubing and immersed in a conventional silicone oil bath, was realized *via* a simple T-piece. In order to maintain control of the system, a back-pressure regulator was placed at the end of the line, either in form of a conventional mechanical spring-

based device, or in form of PEEK capillary of defined length. An initially chemically favored option of a heterogeneous acid catalysis by means of Amberlyst in a column reactor was abandoned in light of the limited usefulness only in case of hydrazine hydrochlorides in batch screenings. Anticipating downstream modifications of the indolenins, we refrained from using AcOH in the flow process, since its removal especially in higher quantities might pose a hurdle. EtOH was determined as master solvent system. In a first attempt, a 0.25 M solution of phenylhydrazine in EtOH was mixed with a solution containing a mixture of 1.0 equivalent aldehyde and 2.0 equivalents HCl, added in form of a 2 M ethanolic HCl solution, as acid catalyst in EtOH. The solutions were transferred from the sample loops into the flow system using a flow rate of 0.5 mL/min for each pump. After a residence time of 15 minutes in the tubular reactor heated to 80° C, the product stream was collected. GC-MS-based analysis indicated full conversion with formation of the desired indolenine to 51% (Table 2, entry 1). Analysis also confirmed formation of the diethyl acetal of the aldehyde that was *a priori* expected given the chosen mode of reagent preparation and regarded unproblematic. A change in residence times did not increase the abundance of the desired product (Table 2, entries 2 and 3), but led to an increased formation of the byproducts.

**Table 2** Optimisation of reaction conditions in flow for the preparation of 3,3-disubstituted indolenines **8a-c**.


| Entry | PhNHNH <sub>2</sub> | X               | Ansatz reagents <sup>[a]</sup> | added eq. HCl | Solvent                             | Flow Rate (mL/min) | Time (min)        | p (bar) | Yield (%) <sup>[b]</sup>                                     |
|-------|---------------------|-----------------|--------------------------------|---------------|-------------------------------------|--------------------|-------------------|---------|--|
| 1     | free base           | <i>N</i> -Boc   | A                              | 2.0           | EtOH                                | 1.0                | 15                | 1.7     | 51 <sup>[c]</sup> (12) <sup>[d]</sup><br>(12) <sup>[e]</sup> |
| 2     | free base           |                 | A                              | 2.0           | EtOH                                | 0.7                | 21                | 1.7     | 31 <sup>[c]</sup> (16) <sup>[d]</sup><br>(17) <sup>[e]</sup> |
| 3     | free base           |                 | A                              | 2.0           | EtOH                                | 0.5                | 30                | 1.7     | 23 <sup>[c]</sup> (19) <sup>[d]</sup><br>(5) <sup>[e]</sup>  |
| 4     | free base           |                 | B                              | 2.2           | EtOH                                | 1.0                | 15                | 1.7     | 86   |
| 5     | HCl salt            |                 | D                              | 1.2           | EtOH                                | 1.0                | 15                | 1.7     | 87   |
| 6     | HCl salt            |                 | C                              | 1.0           | EtOH/AcOH 1:1                       | 1.0                | 15                | 1.7     | ---  |
| 7     | HCl salt            |                 | C                              | 1.0           | <i>n</i> -PrOH/H <sub>2</sub> O 2:1 | 0.7                | 21                | 1.7     | 23 <sup>[c]</sup> (23) <sup>[d]</sup><br>(40) <sup>[e]</sup> |
| 8     | HCl salt            |                 | C                              | 1.0           | EtOH/H <sub>2</sub> O 2:1           | 0.5                | 30                | 1.7     | 4 <sup>[c]</sup> (26) <sup>[d]</sup><br>(45) <sup>[e]</sup>  |
| 9     | free base           | CH <sub>2</sub> | A                              | 2.0           | EtOH                                | 1.0                | 10 <sup>[f]</sup> | 6.9     | 39 (17) <sup>[d]</sup><br>(15) <sup>[e]</sup>                |
| 10    | free base           |                 | A                              | 2.0           | EtOH                                | 0.5                | 20 <sup>[f]</sup> | 1.7     | 18 <sup>[c]</sup> (4) <sup>[d]</sup><br>(52) <sup>[e]</sup>  |
| 11    | free base           |                 | A                              | 2.0           | EtOH                                | 1.0                | 15                | 1.7     | 54 <sup>[c]</sup> (16) <sup>[d]</sup><br>(20) <sup>[e]</sup> |
| 12    | free base           |                 | A                              | 3.0           | EtOH                                | 1.0                | 15                | 1.7     | 10 <sup>[c]</sup>  |
| 13    | free base           |                 | B                              | 2.0           | EtOH                                | 1.0                | 15                | 1.7     | 53 <sup>[c]</sup> (28) <sup>[e]</sup>                        |
| 14    | free base           |                 | B                              | 2.2           | EtOH                                | 1.0                | 15                | 1.7     | 74   |
| 15    | HCl salt            | <i>N</i> -Cbz   | D                              | 1.2           | EtOH                                | 1.0                | 15                | 1.7     | 74   |

[a] Method A: Sample loop (SL) A: 0.5 mmol aldehyde + equiv. HCl in 2 mL of EtOH, SL B: 0.5 mmol PhNHNH<sub>2</sub> in 2 mL of EtOH; Method B: SL A: 0.5 mmol aldehyde + 0.5 mmol PhNHNH<sub>2</sub> in 2 mL of EtOH, SL B: equiv. HCl in 2 mL of EtOH; Method C: SL A: 0.5 mmol aldehyde + (equiv.-1) HCl in 2 mL of EtOH, SL B: 0.5 mmol PhNHNH<sub>2</sub>·HCl in 2 mL of EtOH; Method D: 0.5 mmol aldehyde + 0.5 mmol PhNHNH<sub>2</sub>·HCl in 2 mL of EtOH, heated to 50° C for 5 min prior to loading into the SL, SL B: (equiv.-1) HCl in 2 mL of EtOH. [b] Isolated yield. [c] Conversion ratio as determined by standardized GC-MS analysis. [d] Conversion ratio of diethylacetale by-product as determined by standardized GC-MS analysis. [e] Conversion ratio of arylhydrazone by-product as determined by standardized GC-MS analysis. [f] Reactor volume decreased to 10 mL.

The reagent preparation was hence drastically changed in a way to ensure a perfect mixing of the reagents right from the beginning without the need of a dedicated mixing device: phenylhydrazine and aldehyde were premixed in EtOH in equimolar ratio at a concentration of 0.25 M, and the mixture immediately loaded in the first sample loop. The second sample loop was filled with a 0.275 M solution of ethanolic

HCl. After 15 minutes of residence time at 80° C resulted in 86% of desired product in the GC-MS analysis (Table 2, entry 4). The result could be essentially confirmed replacing the free phenylhydrazine with its hydrochloride salt, reducing in turn the amount of ethanolic HCl by 1 equivalent (Table 2, entry 5). When preparing the aldehyde-hydrazine mixture for the sample loop, the solubility issue arising from the use of the hydrochloride could be circumvented by heating the mixture for approx. 5 minutes in a water bath at 50° C, which obviously triggered an onset of the hydrazine formation thanks to the presence of the acid, leading to the formation of a stable solution suitable for injection into the sample loop. Under otherwise unchanged conditions, the desired product was obtained in 87% (GC-MS). Importantly, the last two experiments indicate that initial condensation is not an issue in the flow approach; it is not necessary to pre-condensate prior to entering the flow reactor. When trying to resolve the insolubility issue without triggering pre-condensation, but by adding a co-solvent during reagent solubilisation, such as water or AcOH, product formation significantly declined (Table 2, entries 6-8).

Reagent preparation strategies could be validated reacting other aldehydes. Premixing aldehyde and phenylhydrazine, and increasing the excess of HCl by 10% resulted in noteworthy conversions into the desired indolenines (Table 2, entries 4,5,14,15). The dynamic window of the transformation with respect to the acid content is rather limited. Increasing the excess by 50% led to a noticeable drop in product formation. (Table 2, entry 12).

The functional set-up and the validated mode of preparing the starting solutions by premixing aldehyde and hydrazine, with eventual warming in case the hydrazine is used as hydrochloride, were subsequently used for the generation of a representative library of indolenines in flow (Table 3). Given that most of the indolenines suffer from an intrinsic instability, we decided, however, to not isolate the indolenine itself, but to directly reduce it to the corresponding stable indoline system. To this end, we simply collected the stream exiting the flow reactor in a conventional flask containing a suspension of an eight-fold molar excess of sodium borohydride in EtOH. Approx. 15 minutes after finishing collecting the flow-born indolenine, conventional aqueous quench and work-up of the reduction yielded reliably the indoline

across the bench of structural motifs tested in this work (Table 3). Overall, higher yields were obtained for the cyclic aldehydes. Variations in the substitution pattern of the hydrazine are well tolerated by and large.

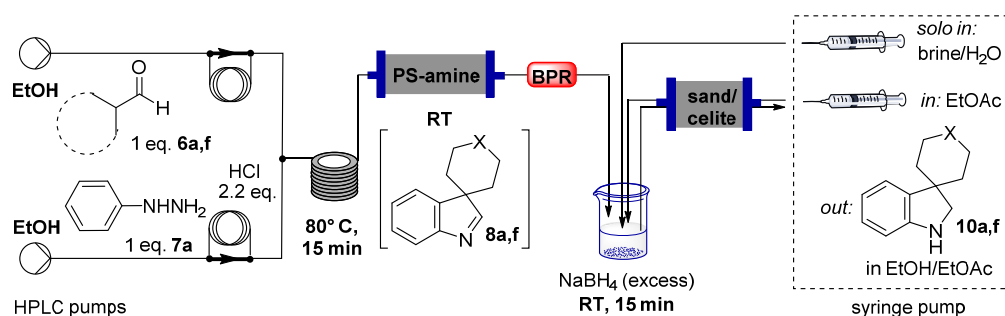
**Table 3** Continuous-flow synthesis of 3,3-disubstituted indolines **10a-i**.

| Entry | Ansatz reagents | Aldehyde/Ketone | Hydrazine | Product | Yield (%)                              |
|-------|-----------------|-----------------|-----------|---------|--|
| 1     | D               |                 |           |         | 92 <sup>[a]</sup><br>58 <sup>[b]</sup> |
| 2     | D               |                 |           |         | 87 <sup>[a]</sup><br>58 <sup>[b]</sup> |
| 3     | D               |                 |           |         | 79 <sup>[a]</sup><br>55 <sup>[b]</sup> |
| 4     | D               |                 |           |         | 61 <sup>[a]</sup><br>43 <sup>[b]</sup> |
| 5     | B               |                 |           |         | 37 <sup>[a]</sup><br>76 <sup>[b]</sup> |
| 6     | B               |                 |           |         | 58 <sup>[a]</sup><br>56 <sup>[b]</sup> |
| 7     | B               |                 |           |         | 44 <sup>[b]</sup>                      |
| 8     | D               |                 |           |         | 50 <sup>[b]</sup>                      |
| 9     | D               |                 |           |         | 46 <sup>[b]</sup>                      |

[a] Yield of the indolenine calculated via GC-MS; [b] Yield of the corresponding indoline after purification by column chromatography.

### Generation of indoline reservoir solutions in telescoped segmented continuous flow

We are ultimately interested in using both the indolenins and indolines as starting point for more complex structures. To this end, the flow protocol was exemplarily modified and extended into telescoped segmented continuous flow protocol in order to host the reduction step. Using an H-cube, reduction of the indolenines in ethanolic solution, after eventual removal of the acid *via* a simple catch-and-release protocol should be feasible. However, following our aim of exploiting advantages offered by flow approaches without the use of eventually expensive dedicated equipment, we decided to stick to the well-working borohydride-based reduction. In a first trial, we extended thus the flow sequence by a column reactor filled with polymer-supported tris(2-aminoethyl)amine to remove both the HCl and eventually unreacted aldehyde from the stream exiting the tubular reactor, and by a subsequent column filled with polymer-supported borohydride. While pH control confirmed the effectiveness of the acid removal step, GC-analysis revealed that imine reduction was not successful. Variation of flow rate or heating the reduction column did not change the situation; only traces of indoline were formed. We thus abandoned the polymer-supported reagent and designed a segmented two-step process depicted in Figure 3.



**Fig. 3** Two-step segmented continuous flow process to indolines.

In this set-up, the HCl and unreacted aldehyde were removed by a column filled with an excess of polymeric tris(2-aminoethyl)amine that was placed inline following the tubular reactor. The purified ethanolic indolenine stream was collected as before in a vessel presenting sodium borohydride suspended

in a minimum of ethanol (2 mL). Having liberated the product stream from acid and aldehyde, it was possible to reduce the excess of reductant by two third. Since reduction was found to be very fast for the indolenines, the reaction was quenched 5 minutes after indolenine collection was finalized, by simultaneous addition of an aqueous phase consisting of 50% brine and ethyl acetate as organic solvent, in a ratio of 1:0.5, respectively. The volume of the aqueous phase was chosen to be equal to the volume of collected in the reduction vessel, since these conditions guaranteed phase separation after completion of addition. Addition of the two work-up solutions was achieved using a programmable syringe pump. 5 minutes after addition the pumping direction of the syringe pump was reversed, and 90% of the organic phase, now consisting of ethyl acetate and ethanol, were withdrawn from the vessel back into the syringe. In order to dry the organic phase, a plastic chromatography column filled with a 1:1 (m/m) mixture of dried celite and sand was placed between the syringe and the tube leading to the vessel (Figure 3). Using this set-up, it was possible to generate a reservoir solution of indolines **10a** and **10f** that each contain as only impurity the respective uncyclised hydrazone. The telescoped approach allowed generation of the target compounds consuming a total of only 12 mL ethanol and 5 mL of ethyl acetate on a 0.5 mmol scale with minimum manual handling or intervention.

## Conclusions

In summary, we have developed a flow chemistry protocol for the synthesis of 3,3-disubstituted indolenines through interrupted Fischer indolisation reaction. Our screening and systematic optimization of a variety of reaction conditions (reagent mixing, temperature, residence time) led to the identification of a reliable protocol which allowed a straightforward and scalable route for the preparation of 3,3-disubstituted indolenines. We further broadened the scope of the conceived methodology by developing a two-step segmented continuous flow process involving an additional heterogeneous in-line

reduction of the indolenines to their indoline counterparts. This telescoped approach allowed generation of the target compounds with limited solvent consumption for both reaction and work-up procedures and required minimum operator input. This newly developed protocol also displays the potential to turn into an effective coupling point for additional flow reactions for multistep syntheses.

## Experimental

### *General comments*

All reagents and chemicals were purchased from Sigma Aldrich-Merck, Zentek or Carlo Erba and used without further purification. TLC analysis was conducted using aluminium foil supported thin-layer silica gel chromatography plates (F254 indicator). Column chromatography was performed using 230–400 mesh, 60 Å pore diameter silica gel using mixtures of ethyl acetate (EA) and hexane (H) or petroleum ether (P).

### *Synthesis of indolenines in batch (General Procedure (GP)-I)*

*tert-Butyl spiro[indole-3,4'-piperidine]-1'-carboxylate (8a)*. A stirred solution of 1-Boc-piperidine-4-carboxaldehyde (108 mg, 0.5 mmol) and phenylhydrazine (50  $\mu$ L, 0.5 mmol) in AcOH (3 mL) was heated to 80 °C for 2 h. After completion of the reaction, AcOH was removed *in vacuo* and the residue was diluted with EtOAc (5 mL) and a saturated solution of NaHCO<sub>3</sub> was added. The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel (EA/P 1:4) obtaining **8a** as a red oil. Yield: 104 mg (73%).

### ***Reduction of indolenines in batch (GP-II)***

***tert-Butyl spiro[indoline-3,4'-piperidine]-1'-carboxylate (10a)***. To a solution of **8a** (45 mg, 0.16 mmol) in MeOH (3 mL), NaBH<sub>4</sub> (30 mg, 0.8 mmol) was added. The reaction was kept stirring for 3 h at 50° C. Then reaction was quenched with a saturated solution of NaHCO<sub>3</sub> (10 mL), MeOH was removed under reduced pressure and residue was dissolved with EtOAc and washed with dist. water (3 × 10 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and solvents removed *in vacuo* to give a residue which was purified by flash column chromatography on silica gel (EA/P 1:4) obtaining **10a** as orange solid. Yield: 37 mg (80%).

### ***Synthesis of indolenines in flow (GP-III)***

Chemical transformations in flow were realized using a self-made flow reactor: two Waters 510 HPLC pumps were connected each to a Rheodyne 9010 injection valves, each equipped with a 2 mL sample loop made from PTFE tubing and an injection port for disposable syringes. The injection valves were further connected *via* a T-piece to a coiled PTFE tubing of 15 mL volume. The coil was immersed in a silicone oil bath for controlling reaction temperatures. The tubular reactor finished into a back pressure regulator (BPR), which was either spring mechanism-based (6.7 bar) or simply a PEEK capillary of defined length (1.7 bar). Product containing exiting streams were collected directly in a flask. An aliquot of the collected phase was used for analysis by GC-MS. Reagents were prepared for loading into the sample loops according to one of the following four methods: Method A: Sample loop (SL) A: 0.5 mmol aldehyde + equiv. HCl in 2 mL of EtOH, SL B: 0.5 mmol PhNHNH<sub>2</sub> in 2 mL of EtOH; Method B: SL A: 0.5 mmol aldehyde + 0.5 mmol PhNHNH<sub>2</sub> in 2 mL of EtOH, SL B: equiv. HCl in 2 mL of EtOH; Method C: SL A: 0.5 mmol aldehyde + (equiv.-1) HCl in 2 mL of EtOH, SL B: 0.5 mmol PhNHNH<sub>2</sub>•HCl in 2 mL of EtOH; Method D: 0.5 mmol aldehyde + 0.5 mmol PhNHNH<sub>2</sub>•HCl in 2 mL of EtOH, heated to 50° C for 5 min prior to loading into the SL, SL B: (equiv.-1) HCl in 2 mL of EtOH.

### ***Synthesis of indolines in flow-batch combination (GP-IV)***

Indolines were realized using the above described flow set-up, collecting the exiting, indolenine-containing stream in a flask held at 0° C and typically prepared with 142 mg (3.75 mmol, 7.5 equiv.) of sodium borohydride for a standard 0.5 mmol indolenine production in flow. 15 minutes after finishing collecting the indolenine product stream, the flask was allowed to gradually warm up to room temperature. Aqueous quench and work-up was achieved adding sodium bicarbonate solution, followed by three-fold extraction of the aqueous phase with an equal volume of ethyl acetate. The organic phase was dried over magnesium sulphate and concentrated *in vacuo*. Crude products were purified over silica gel.

### ***Generation of indoline solutions in telescoped segmented continuous flow***

Indolines were realized using the above described flow set-up with the following modifications: an Omnifit column (10 mm i.d. x 100 mm) filled with 1 g (3.5 – 5.0 mmol/g loading) of polymer-supported tris(2-aminoethyl)amine was placed in-line between to the outlet of the PTFE reactor coil and the 1.7 bar BPR. The exiting stream was collected in a slim becher kept at RT and equipped with 47 mg (1.25 mmol, 2.5 equiv.) sodium borohydride in 1 mL EtOH. 5 minutes after collection of indolenine-containing reaction mixture was finished, a NE-1000 programmable syringe pump was activated to deliver into the beaker 5 mL of ethyl acetate from a glass syringe equipped with activated 4 Å molecular sieve beads, and 10 mL of half-concentrated brine from a disposable syringe. A chromatography column charged with a 1:1 mixture (m/m) of sand and celite was placed in-line between the glass column and the capillary used for directing the organic solvent into the beaker and for aspirating the organic phase again: approx. 2 minutes after addition of these phases, magnetic agitation was stopped and phases were allowed to

separate. The syringe pump was subsequently activated in reverse mode to aspire 90-95% of the organic phase.

### ***NMR analyses***

*<sup>1</sup>H NMR measurements:* An accurately weighed amount of analyte (about 5.0 - 10.0 mg) was dissolved in 600  $\mu$ L of deuterated chloroform ( $\text{CDCl}_3$ ) or dimethyl sulfoxide ( $\text{DMSO-}d_6$ ). The mixture was transferred into a 5 mm NMR tube. The spectra were acquired on a Bruker 400 MHz spectrometer using the standard Bruker zg sequence (32 scans at 20° C). NMR data were processed with MestreNova (Version 8.1.1, Mestrelab Research).

*<sup>13</sup>C NMR measurements:* An accurately weighed amount of analyte (about 35.0 mg) was dissolved in 600  $\mu$ L of deuterated chloroform ( $\text{CDCl}_3$ ). The mixture was transferred into a 5 mm NMR tube. The spectra were acquired on a Bruker 400 MHz spectrometer using the standard Bruker zgpg30 sequence (3072 scans at 20° C). NMR data were processed with MestreNova (Version 8.1.1, Mestrelab Research).

### ***GC-MS analysis***

Purified samples were dissolved in ethyl acetate at concentrations between 0.5 and 1.0 mg/mL. Analysis of reaction mixtures were performed after a quick work-up of a 1 mL aliquot: the reaction mixture was brought to pH 8 by addition of conc. sodium bicarbonate solution. The aqueous solution was subsequently extracted once with 1.0 to 1.5 mL of ethyl acetate. The organic phase was separated and dried over magnesium sulphate. Solids were pelleted by centrifuging, and a 0.5 mL aliquot of the organic phase was subjected to analysis. Gas chromatographic separation of the samples was achieved using an Agilent Technologies 5973N GC/MS System equipped with 7683 ALS Automatic Liquid Sampler Autoinjector. A Supelco fused-silica capillary column SLBTM-5ms (30m long, 0.25 mm thick, 0.25  $\mu$ m diameter) was

used as stationary phase, He (UHP grade) as mobile phase; the system was operated in 'linear velocity mode' with a starting pressure of 100 kPa, 280° C injection temperature, and 200° C interface temperature, running as temperature program: 50° C start temperature for 1 min, 10° C/min heating rate, 280° C final temperature for 5 min). System control and analyses were realised using the Agilent ChemStation software package (Version X).

### ***Product characterization***

***tert*-Butyl spiro[indoline-3,4'-piperidine]-1'-carboxylate (10a).** According to GP-D, a mixture of phenylhydrazine salt **7a** (73 mg, 0.5 mmol) and 1-Boc-piperidine-4-carboxaldehyde **6a** (108 mg, 0.5 mmol) was treated with HCl (300  $\mu$ L, 0.6 mmol) before sodium borohydride (144 mg, 3.82 mmol) was added. Yield: 83 mg (58%); orange solid;  $R_f$  = 0.4 (H:E = 7:3).  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.01 – 6.96 (m, 2H), 6.67 (td,  $J$  = 7.4, 1.0 Hz, 1H), 6.58 (dd,  $J$  = 7.3, 1.0 Hz, 1H), 4.07 – 3.92 (m, 2H), 3.41 (s, 2H), 2.92 – 2.80 (m, 2H), 1.77 – 1.69 (m, 2H), 1.67 – 1.60 (m, 2H), 1.42 (s, 9H). GC-MS (EI, 70 eV):  $m/z$  (%) = 286  $[\text{M}]^+$ ;  $t_R$  = 20.87 min. NMR data are in agreement with reported data.<sup>36</sup>

**Spiro[cyclohexane-1,3'-indoline] (10b).** According to GP-D, a mixture of phenylhydrazine salt **7a** (73 mg, 0.5 mmol) and cyclohexanecarboxaldehyde **6b** (59  $\mu$ L, 0.5 mmol) was treated with HCl (300  $\mu$ L, 0.6 mmol) before sodium borohydride (144 mg, 3.82 mmol) was added. Yield: 54 mg (58%); yellow solid;  $R_f$  = 0.6 (H:E = 7:3).  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.00 – 6.92 (m, 2H), 6.67 (td,  $J$  = 7.4, 1.0 Hz, 1H), 6.57 (dt,  $J$  = 7.7, 0.8 Hz, 1H), 3.35 (s, 2H), 1.70 – 1.61 (m, 5H), 1.55 – 1.47 (m, 2H), 1.37 – 1.25 (m, 3H). GC-MS (EI, 70 eV):  $m/z$  (%) = 187  $[\text{M}]^+$ ;  $t_R$  = 14.94 min. NMR data are in agreement with reported data.<sup>27</sup>

**Benzyl spiro[indoline-3,4'-piperidine]-1'-carboxylate (10c).** According to GP-D, a mixture of phenylhydrazine salt **7a** (73 mg, 0.5 mmol) and 4-formyl-*N*-Cbz-piperidine **6c** (103  $\mu$ L, 0.5 mmol) was treated with HCl (300  $\mu$ L, 0.6 mmol) before sodium borohydride (144 mg, 3.82 mmol) was added. Yield:

88 mg (55%); yellowish solid;  $R_f = 0.25$  (H:E = 7:3).  $^1\text{H NMR}$  (400 MHz, Chloroform- $d$ )  $\delta$  7.33 – 7.25 (m, 5H), 7.01 – 6.95 (m, 2H), 6.68 (td,  $J = 7.4, 1.0$  Hz, 1H), 6.58 (dd,  $J = 7.8, 0.8$  Hz, 1H), 5.09 (s, 2H), 4.12 – 4.02 (m, 2H), 3.42 (s, 2H), 2.99 – 2.88 (m, 2H), 1.67 – 1.46 (m, 4H). GC-MS (EI, 70 eV):  $m/z$  (%) = 322  $[\text{M}]^+$ ;  $t_R = 26.34$  min. NMR data are in agreement with reported data.<sup>36</sup>

**2',3',5',6'-Tetrahydrospiro[indoline-3,4'-pyran] (10d).** According to GP-D, a mixture of phenylhydrazine **7a** (50  $\mu\text{L}$ , 0.5 mmol) and tetrahydropyran-2H-4-carbaldehyde **6d** (54  $\mu\text{L}$ , 0.5 mmol) was treated with HCl (600  $\mu\text{L}$ , 1.2 mmol) before sodium borohydride (144 mg, 3.82 mmol) was added. Yield: 42 mg (43%); yellow solid;  $R_f = 0.4$  (H:E = 7:3).  $^1\text{H NMR}$  (400 MHz, Chloroform- $d$ )  $\delta$  7.03 (dd,  $J = 7.4, 1.3, 0.6$  Hz, 1H), 6.98 (td, 1H), 6.70 (td, 1H), 6.59 (dd, 1H), 3.94 – 3.86 (m, 2H), 3.53 – 3.46 (m, 4H), 1.96 – 1.88 (m, 2H), 1.60 (dd,  $J = 13.7, 2.3$  Hz, 2H). GC-MS (EI, 70 eV):  $m/z$  (%) = 189  $[\text{M}]^+$ ;  $t_R = 15.39$  min. NMR data are in agreement with reported data.<sup>37</sup>

**3-Methyl-3-propylindoline (10e).** According to GP-D, a mixture of phenylhydrazine **7a** (50  $\mu\text{L}$ , 0.5 mmol) and 2-methylvaleraldehyde **6e** (63  $\mu\text{L}$ , 0.5 mmol) was treated with HCl (600  $\mu\text{L}$ , 1.2 mmol) before sodium borohydride (144 mg, 3.82 mmol) was added. Yield: 46 mg (52%); yellowish liquid;  $R_f = 0.7$  (H:E = 7:3).  $^1\text{H NMR}$  (400 MHz, Chloroform- $d$ )  $\delta$  7.00 – 6.89 (m, 2H), 6.66 (dd,  $J = 7.4, 1.0$  Hz, 1H), 6.56 (dt,  $J = 7.6, 0.9$  Hz, 1H), 3.33 (d,  $J = 8.8$  Hz, 1H), 3.17 (d,  $J = 8.8$  Hz, 1H), 1.51 (t, 2H), 1.21 (s, 3H), 1.19 – 1.12 (m, 2H), 0.81 (t,  $J = 7.3$  Hz, 3H). GC-MS (EI, 70 eV):  $m/z$  (%) = 175  $[\text{M}]^+$ ;  $t_R = 11.81$  min. NMR data are in agreement with reported data.<sup>27</sup>

**3,3-Diethylindoline (10f).** According to GP-D, a mixture of phenylhydrazine **7a** (50  $\mu\text{L}$ , 0.5 mmol) and 2-ethylbutiraldehyde **6f** (64  $\mu\text{L}$ , 0.5 mmol) was treated with HCl (600  $\mu\text{L}$ , 1.2 mmol) before sodium borohydride (144 mg, 3.82 mmol) was added. Yield: 49 mg (56%); yellowish liquid;  $R_f = 0.6$  (H:E = 7:3).  $^1\text{H NMR}$  (400 MHz, Chloroform- $d$ )  $\delta$  6.95 (td,  $J = 7.6, 1.3$  Hz, 1H), 6.89 (ddd,  $J = 7.4, 1.3, 0.6$  Hz, 1H), 6.64 (td,  $J = 7.4, 1.0$  Hz, 1H), 6.54 (dt,  $J = 7.7, 0.8$  Hz, 1H), 3.27 (s, 2H), 1.71 – 1.59 (m, 2H), 1.59 – 1.48 (m, 2H), 0.75 (t,  $J = 7.5$  Hz, 6H). GC-MS (EI, 70 eV):  $m/z$  (%) = 175  $[\text{M}]^+$ ;  $t_R = 11.94$  min. NMR data are in agreement with reported data.<sup>27, 38</sup>

**5-Chloro-3,3-diethylindoline (10g).** According to GP-D, a mixture of 4-chloro-phenylhydrazine salt **7b** (91 mg, 0.5 mmol) and ethylbutyraldehyde **6f** (63  $\mu$ L, 0.5 mmol) was treated with HCl (300  $\mu$ L, 0.6 mmol) before sodium borohydride (144 mg, 3.82 mmol) was added. Yield: 46 mg (44%); yellow liquid;  $R_f$  = 0.6 (H:E = 7:3).  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  6.90 (dd,  $J$  = 8.2, 2.2 Hz, 1H), 6.82 (d,  $J$  = 2.1 Hz, 1H), 6.45 (d,  $J$  = 8.2 Hz, 1H), 3.30 (s, 2H), 1.62 – 1.51 (m, 4H), 0.75 (t,  $J$  = 7.5 Hz, 6H). GC-MS (EI, 70 eV):  $m/z$  (%) = 209  $[\text{M}]^+$ ;  $t_R$  = 14.63 min.

**Benzyl 5-chlorospiro[indoline-3,4'-piperidine]-1'-carboxylate (10h).** According to GP-D, a mixture of 4-chlorophenylhydrazine salt **7b** (91 mg, 0.5 mmol) and 4-Formyl-*N*-Cbz-piperidine **6c** (103  $\mu$ L, 0.5 mmol) was treated with HCl (300  $\mu$ L, 0.6 mmol) before sodium borohydride (144 mg, 3.82 mmol) was added. Yield: 89 mg (50%); yellowish liquid;  $R_f$  = 0.2 (H:E = 7:3).  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.34 – 7.27 (m, 5H), 6.92 (dd,  $J$  = 8.2, 2.2 Hz, 1H), 6.88 (d,  $J$  = 2.1 Hz, 1H), 6.47 (d,  $J$  = 8.2 Hz, 1H), 5.09 (s, 2H), 4.14 – 4.01 (m, 2H), 3.42 (s, 2H), 2.96 – 2.84 (m, 2H), 1.73 – 1.62 (m, 4H). GC-MS (EI, 70 eV):  $m/z$  (%) = 356  $[\text{M}]^+$ ;  $t_R$  = 34.29 min. NMR data are in agreement with reported data.<sup>39</sup>

**Benzyl 7-methylspiro[indoline-3,4'-piperidine]-1'-carboxylate (10i).** According to GP-D, a mixture of *o*-tolylphenylhydrazine salt **7c** (80 mg, 0.5 mmol) and 4-Formyl-*N*-Cbz-piperidine **6c** (103  $\mu$ L, 0.5 mmol) was treated with HCl (300  $\mu$ L, 0.6 mmol) before sodium borohydride (144 mg, 3.82 mmol) was added. Yield: 78 mg (46%); yellowish liquid;  $R_f$  = 0.2 (H:E = 7:3).  $^1\text{H}$  NMR (400 MHz, Chloroform-d)  $\delta$  7.32 – 7.22 (m, 5H), 6.87 – 6.80 (m, 2H), 6.63 (t,  $J$  = 7.4 Hz, 1H), 5.09 (s, 2H), 4.16 – 4.00 (m, 2H), 3.43 (s, 2H), 3.05 – 2.85 (m, 2H), 2.06 (s, 3H), 1.78 – 1.61 (m, 4H).  $^{13}\text{C}$  NMR (101 MHz, Chloroform-d)  $\delta$  155.4, 148.9, 136.9, 135.5, 129.0, 128.5, 128.0, 127.9, 120.1, 119.3, 119.1, 77.4, 77.1, 76.7, 67.2, 55.9, 44.7, 41.3, 39.6, 35.8, 16.7. GC-MS (EI, 70 eV):  $m/z$  (%) = 336  $[\text{M}]^+$ ;  $t_R$  = 27.11 min.

## Conflicts of interest

There are no conflicts to declare.

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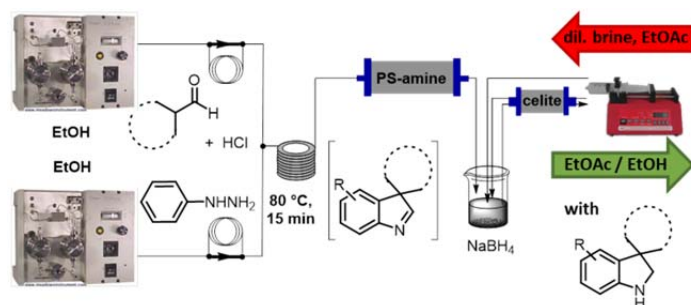
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## TOC graphic



3,3-disubstituted indolenines are obtained *via* a green and sustainable flow chemistry protocol for interrupted Fischer indolisation reactions.