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Photocyclization of enamines to access Spiroindolines and Spirooxindoles in continuous flow

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ABSTRACT

We report an expedited flow chemistry approach to the catalyst/photosensitizer-free UV photocyclizations of aryl-enamines to afford spiroindolines. The photocyclizations occur under mild conditions and are tolerant to a variety of substituted aryl-enamines and spirocycle ring sizes. This flow protocol has a wide substrate scope and addresses the problems of irreproducibility and scalability of batch protocols. The utility of this reaction is demonstrated in a shortened formal synthesis of (±)-horsfiline.

Introduction

Spiroindolines and spirooxindoles are featured in the core of numerous natural products, chemotherapeutics and drug molecules (Scheme 1) [1]. Increasingly, as this scaffold is observed in molecules with biological significance, there is growing value to develop new practical methods to access such scaffolds.

In 1984, Schultz and co-workers reported the UV promoted 6e-photocyclization of aryl-enamines to spiroindolines (Scheme 2) [2]. To the best of our knowledge, this is the only known synthesis of compounds with substructure **A** [3]. This transformation could be of great value, especially to medicinal chemistry projects, as it allows for the generation of diversity at four areas of the scaffold from readily available starting materials (anilines and keto esters). This strategy could also provide a practical way of generating novel spiro compounds, which are becoming increasing utilized in medicinal chemistry due to their inherent three dimensionality and structural novelty [4]. Since Schultz's early work, there have been no reports of developing and exploring this reaction further. In our laboratories, the batch photocyclization of aryl-enamines to spiroindolines were often hampered by extended reaction times, batch-to-batch variability and poor conversions, problems that are very common in batch photochemical reactions. Flow chemistry offers a number of synthetic advantages when applied to photochemistry in part owing to precise heat control, superior/consistent light penetration, controlled exposure time, inherent scalability and integration with additional parameter control (heating/cooling/reagent addition) [5]. We sought to explore the scope of this UV-photocyclization under flow conditions and its utility in accessing spiroindolines.

Results and discussion

The Schiff base derived from aniline and ethyl-2-cyclopentyl-2-oxoacetate was used as a model system to optimize the photocyclization conditions (**1**, Table 1). Initial solvent and light source screening in batch revealed that dioxane or benzene with either UV-A or UV-B gave the best yields (Entries 1 (45%), **2** (42%) and **3** (38%)). These reactions required > 16 h to reach full conversion on a 1 mmol scale and 2 days on 5 mmol scale.

In flow, it was found that the corresponding cyclization occurred rapidly (<0.5 h irradiation time, 0.3–0.5 mmol). The wavelength of light required to facilitate the cyclization seemed to be critical to reaction progression (Table 1). Enamine **1** cyclized smoothly to spiroindoline **2** when irradiated in benzene using a UV-A LED bulb (365 nm λmax) with excellent isolated yield (82%, entry 12). In comparison, the corresponding batch reaction required > 16 h to proceed to full conversion with a lower overall yield (45%, entry 1).

As stated earlier, Schultz's initial report of this transformation provided little information on reaction scope. This limited knowledge of reaction scope, as well as other potential difficulties such as scaling issues and reproducibility, makes this batch reaction unappealing for generating diverse sets of indolines. In order to make this protocol more attractive for generating diverse

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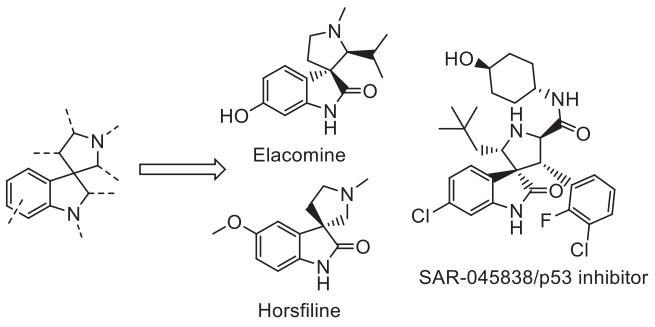
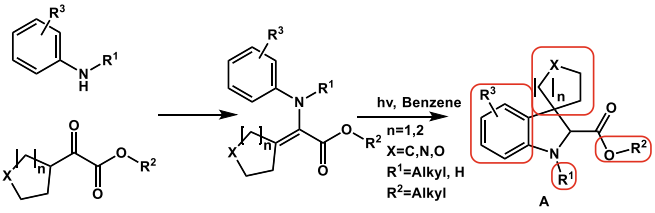


Scheme 1. Spiroindolines in natural products and drug molecules.



Scheme 2. Photocyclization of enamines to spiroindolines.

spiroindolines, an investigation into the scope of this flow protocol was carried out. It was found that aryl-enamines **3** were converted to spiroindolines in good to excellent yields Table 2. Both electron-donating (OMe) and -withdrawing (-F, -Br, –CN) groups were tolerated irrespective of the substitution pattern. *N*-Substituted aryl enamines also cleanly underwent cyclization (**4 j**,**l**). A heteroatom in the spirocycle (**4 l**) was also tolerated. Interestingly, aryl-enamine **3 l** failed to cyclize under batch conditions but was successful under optimal flow conditions, demonstrating that this flow protocol not only increases reaction efficiency but it may also expand the substrate scope of the reaction, an aspect of flow chemistry that is often overlooked [6]. This protocol may also address the scalability issues observed in batch (theoretical daily output of this protocol can exceed 18 g/per day under steady state conditions (compound **4 g**)).

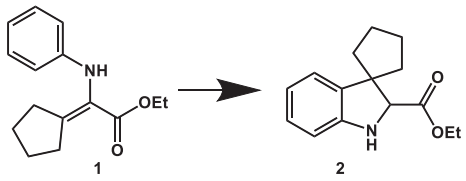
Finally, we turned our attention to the application of this method to the formal synthesis of (±)-horsfiline (Scheme 1 and 3), a natural product with analgesic properties [7]. It was envisaged that our strategy would likely intercept the route previously reported by Fuji and co-workers [8] and could potentially allow for the generation of SAR around four key areas of the scaffold (Scheme 2). Horner-Wadsworth-Emmons (HWE) reagent **5** was prepared according to literature precedent [9]. Treatment of **5** under standard HWE conditions afforded **6** as a mixture of *E/Z* isomers. Olefin **6** was then deprotected with cesium

fluoride to afford keto-ester **7** in moderate yields. Microwave assisted condensation of *N*-benzyl-*p*-anisidine with **7** furnished Schiff base **3 l**. An initial investigation of the photocyclization using UV-A (365 nm) under batch conditions to afford spiroindoline **4 l** was unsuccessful, giving poor conversions even with prolonged reaction times. Interestingly, using the optimal flow conditions, **3 l** was cleanly converted to protected spiroindoline **4 l** in quantitative yield with a 20 min residence time. We observed that basic hydrolysis of the spiroindolines **4** often yielded oxidatively decarboxylated products along with the anticipated acid. It was therefore envisaged that ester **4 l** could be oxidatively decarboxylated to furnish spirooxindole **8** and therefore intercept Fuji's route towards horsfiline. Unfortunately, basic hydrolysis of **4 l** yielded only the corresponding carboxylic acid. However, under aerobic conditions with UV-A irradiation, ester **4 l** was converted to spirooxindole **8** to complete a formal synthesis of (±)-horsfiline. To the best of our knowledge, this is the first example of a UV-promoted oxidative decarboxylation to afford spirooxindoles under mild conditions.

Conclusion

In conclusion, we report an expedited flow chemistry approach to the catalyst/photosensitizer-free UV photocyclizations of aryl-enamines to afford spiroindolines. The photocyclizations occur under mild conditions and are tolerant to a variety of substituted aryl-enamines and spirocycle ring sizes. This flow protocol has a wide substrate scope and addresses the problems of irreproducibility and scalability of batch protocols. The utility of this reaction is demonstrated in a shortened formal synthesis of (±)-horsfiline relative to a previous route described by Fuji and co-workers. Central

Table 1
Reaction optimization for the UV-photocyclization aryl-enamine **1** to spiroindoline **2**.



Entry	UV source	Solvent	Batch/Flow rate (mL/min)	Yield **2** (%)
1	UV-A	PhH	Batch	45
2	UV-B	PhH	Batch	42
3	UV-A	Dioxane	Batch	38
4	UV-A	Cyclohexane	Batch	36
5	UV-A	PhH/MeOH	Batch	18
6	UV-A	PhH/MeCN	Batch	25
7	UV-A	Dioxane/MeOH	Batch	16
9	UV-A[a]	PhH	0.5[b]	45
10	450 nm LED	PhH	0.5[b]	0
11	UV-A/B[a]	PhH	0.5[b]	56
12	**365 nm LED**	**PhH**	**0.5[b]**	**82**

a 100 W medium pressure mercury lamp with Pyrex or 320 nm filter.
b 0.1 M, 0.5 mL/min, 30 °C, 1 bar, 10 mL reaction coil, 20 min residence time

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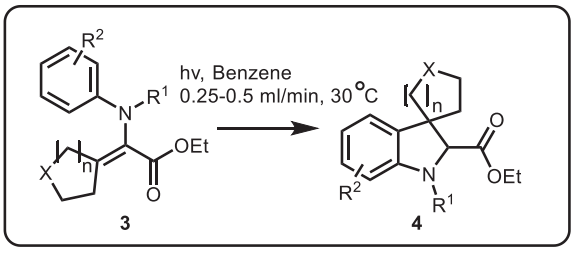
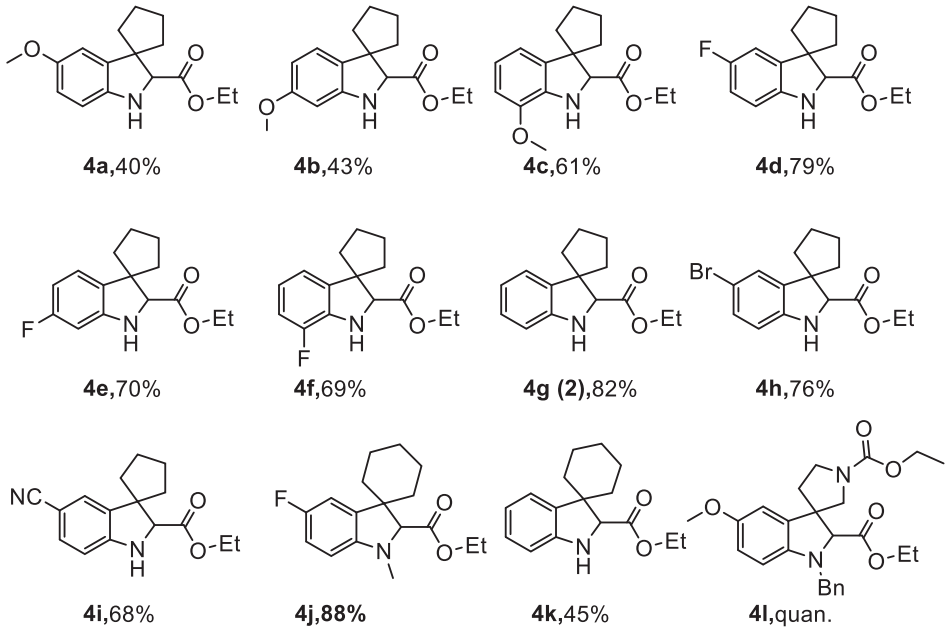
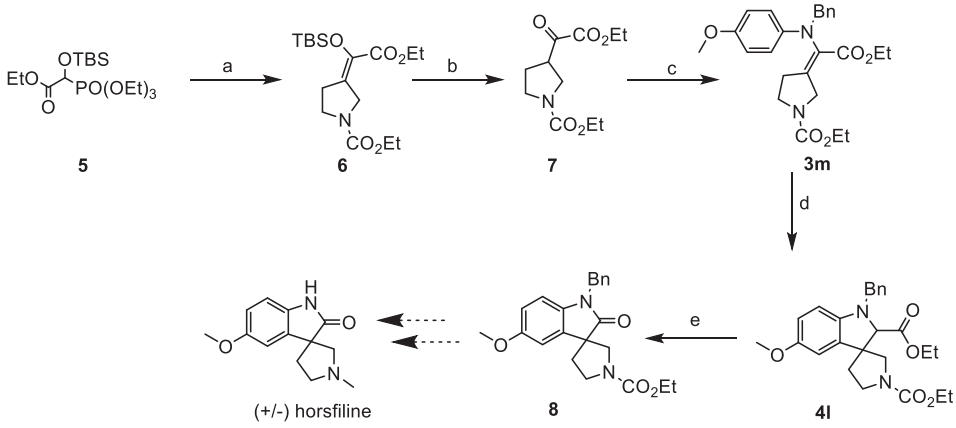
Table 2
UV-photocyclization of aryl-enamine **3** to 2-carboxylspiroindoline **4**.







Scheme 3. Formal synthesis of (±)-horsfiline. Reagents and conditions: a. LiHMDS/ethyl 3-oxopyrrolidine-1-carboxylate, −78 °C to rt, 16 h, 96%. b. CsF/AcOH, 0 °C, 12 h, 79%. c. *N*-benzyl-*p*-anisidine, TFA, $MgSO_4$, 150 °C, PhH, 30 min, 74%. d. UV-A LED (365 nm), 0.5 mL/min (20 min)/0.2 mmol/ hv, PhH, quant. e. LiOH UV-A bulb, air, MeOH/H_2O (2:1), rt, 4 d, 26%.

to the shortened synthesis of (±)-horsfiline is a mild and novel UV-promoted oxidative decarboxylation converting 2-carboxyspiroindolines to spiroox-2-indoles. This method could be used to generate structure activity relationship on the analgesic properties of horsfiline, since it can easily provide diversity at four areas of the scaffold. Our expedient UV-photocyclization represents a rapid method for building complexity from relatively abundant starting materials for alkaloid synthesis. Furthermore, the benefit in accessing synthetically valuable intermediates such as **8** is extended by a novel UV-promoted oxidative decarboxylation which offers a chemical segue between spiroindolines and spirooxindoles warranting the attention of the synthetic community. The scope of this decarboxylative oxidation reaction and application of this method to the synthesis of natural products will be reported in due course.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152111.

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