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Synthesis and Diversification of Chiral Spirooxindoles via Organocatalytic Cascade Reactions †

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Abstract: The synthesis of chiral spirooxindoles through different amino catalytic activation modes is described herein. Several alkenylisatins were obtained from the Knoevenagel reaction of isatin and activated methylene derivatives containing electron withdrawing groups such as ethyl cyanoacetate. A spirooxindole derivative was obtained from the oxa-Michael-Michael reaction between one of the synthesized alkenylisatins and 2-hydroxycinnamaldehyde. Currently, new methodologies that allow access to spirooxindole scaffolds are being explored, mainly though Diels-Alder reactions between 2-methylenindolin-2-ones and aldehydes via the trienamine activation mode. The following cascade reactions will be explored in the future to obtain the proposed polycyclic spirooxindole derivatives.

Keywords: spirooxindoles; organocatalysis; 3-methylenindolin-2-one; ApDOS

1. Introduction

The search for bioactive compounds relies on the ability of synthetic chemists to efficiently prepare molecule libraries with structural, stereochemical and skeletal diversity. Evans coined the term "privileged scaffolds" in the 1980s [1]. These synthetic frameworks can be identified by either their high affinity towards several receptors or by the fact that multiple molecules containing said framework are bioactive. At first, privileged scaffolds were only found within the structure of important natural products; nowadays there are a couple different ways of getting to and determining the activity of new privileged scaffolds [2].

In general, there are two types of methodologies for the obtention of biologically important compounds, TOS, and DOS. Originally, TOS (Target-Oriented Synthesis) was the only methodology used in the search for bioactive compounds though retrosynthetic analysis. Later, DOS (Diversity-Oriented Synthesis) replaced it in many instances; mainly due to its higher ability to create diversity and, therefore, have a higher probability of finding a molecule with promising biological activity. Recently, a new strategy for developing molecule libraries was described; ApDOS (Aminocatalytic privileged Diversity-Oriented Synthesis) which involves a diversification pathway through the aminocatalytic mode instead of the skeletal building blocks [3].

Spirooxindoles are oxindole derivatives that contain a ring fused in a spiro manner at the C-3 atom. Spirooxindoles are a particularly important class of organic moieties due to their significant biological activities, such as anti-tumor, antiviral and antibacterial activities Figure 1 [4]. The synthesis of these heterocycles is a challenge that has especially interested chemists since the last decade.

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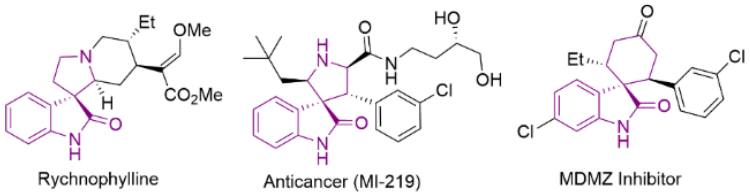
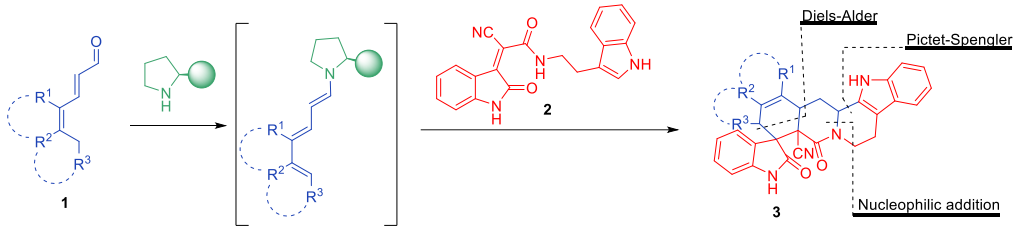


Figure 1. Examples of spirooxindoles.

The synthesis of chiral spirooxindoles through different amino catalytic activation modes is described herein. Once obtained, the spirooxindoles would be submitted to a cascade sequence of reactions (nucleophilic addition/elimination/Pictet–Spengler) to yield polycyclic derivatives such as **3** (Scheme 1).



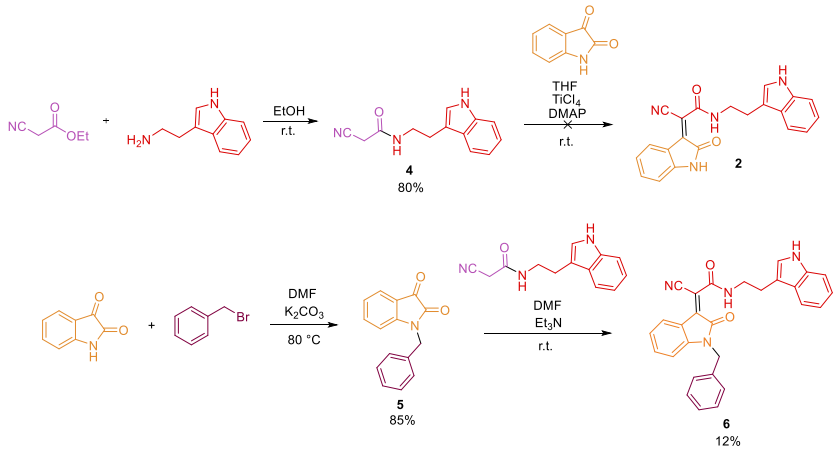
Scheme 1. Project outline.

2. Methods

Proton (^{1}H) NMR spectra were recorded on aBruker UltraShield Plus 500 MHz, Avance III HD (equipment sourced from Bruker Biospin AG; Industriestrasse 26; CH-8117 Fällanden, Switzerland). Flash column chromatography was performed on silica gel using hexane/ethyl acetate as the mobile phase. 3-Methylenindolin-2-ones **7a** and **7b** were synthesized using the reported conditions [5,6].

3. Results and Discussion

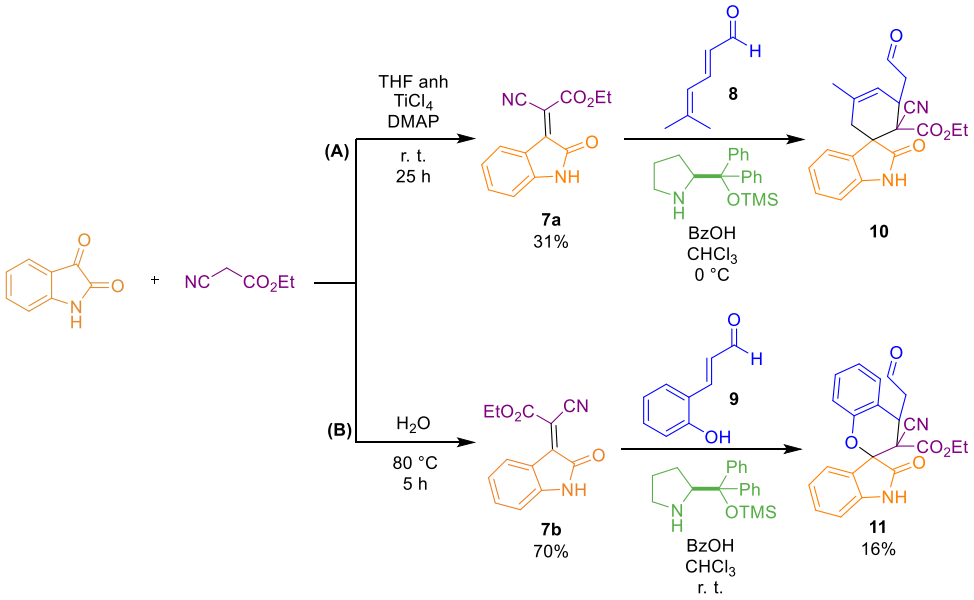
Starting from triptamine and ethyl cyanoacetate, amide **4** was formed with an 80% yield. Then, isatin and **4** were allowed to react under the Knoevenagel condensation conditions reported [5]. However, the desired product (**2**) was not obtained under these conditions, probably because the nitrogen in isatin may be exerting unwanted side reactions and preventing the formation of **2**. Therefore, isatin was protected to *N*-benzyl-isatin in 85% yield. This new isatin derivative reacted, hoping for Knoevenagel condensation under modified conditions from Tiwari's report [6]. 3-Methylenindolin-2-one derivative **6** was obtained with a 12% yield (Scheme 2).



Scheme 2. 3-Methylenindolin-2-one synthesis.

Similarly, Knoevenagel condensation between isatin and ethyl cyanoacetate was performed under two different conditions to yield the two isomers *Z* (**7a**) and *E* (**7b**). Both isomers were used in different aminocatalytic processes to yield spirooxindoles.

The Diels–Alder reaction between dienophile **7a**, aldehyde **8** and Jørgensen–Hayashi catalyst was performed. A product was isolated, but its characterization has not been possible as of now (Scheme 3A).



Scheme 3. 3-Methylenindolin-2-one synthesis and spirooxindole formation. (**A**) Knoevenagel condensation between isatin and ethyl cyanoacetate yielded **7a**, and subsequent organocatalytic Diels-Alder reaction to yield spirooxindole **10**. (**B**) Knoevenagel condensation between isatin and ethyl cyanoacetate yielded **7b**, and organocatalytic oxa-Michael-Michael reaction for the obtention of spirooxindole **11**.

The aminocatalytic oxa-Michael-Michael reaction between **7b** and *o*-hydroxy cinnamaldehyde **9** yielded 16% of the spirooxindole derivative **11** (Scheme 3B).

4. Conclusions

Spirooxindoles are an important class of privileged structures. The search for new synthetic pathways for their constriction has been on the rise within the synthetic organic chemists' community since the last decade. A new spirooxindole derivative was obtained through aminocatalytic activation. The synthesis and diversification of spirooxindole derivatives through Diels–Alder and oxa-Michael-Michael reactions is underway.

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