NIS-Mediated Dearomative Spirocyclisations of Tryptamine-Derived Isocyanides Towards Spiroindolenines and its Application in the Total Synthesis of 19-Oxoaspidospermidine

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Abstract

The spiroindoline and spiroindolenine moieties are common structural features found in many natural products, such as the Aspidosperma alkaloids. The spirocyclic motifs are highly valuable from a medical point of view due to its complexity generating characteristics and biological activity. Therefore, a considerable amount of research has been dedicated to the synthesis of spiro-indole structures. Until this day the dearomatization strategy is applied most frequently, but it is not universal and highly specific structures are obtained. Previous work in our group has shown that the ambiphilic character of isocyanides can be exploited in the synthesis of spiroindolines via a highly diastereoselective interrupted Ugi reaction starting from tryptamine-derived isocyanide. Unlike the conventional Ugi reaction, the nitrilium ion intermediate undergoes an intramolecular attack by the C-3 position of the indole, thereby dearomitisising the indole. Complex spirocyclic architectures were obtained, containing the core of several indole monoterpenoid alkaloids. However, the overall structures are highly specific and cannot be interconverted to other useful products.

In this work, a tryptamine-derived isocyanide based dearomative spirocyclisation has been developed, utilizing N-Iodosuccinimide (NIS) as the electrophile. This results in spiroindolenines containing the imidoyl iodide as functional group. The reaction tolerates a wide range of solvents and mild conditions. The rather exotic imidoyl iodide can be functionalized in order to access architectures containing the spirocyclic motif. Depending on the substitution pattern of the indole, the spiroindolenine imidoyl iodides could be isolated and stored or functionalized in situ. Herein we report unique reactivity accompanied with the spiroindolenine imidoyl iodides, such as reduction of the imidoyl iodide and the imine of the C-2 unsubstituted indolenine in order to access the core of Sky-kinase inhibitors. In addition, reduction of C-2 substituted indolenines went diastereoselective and chemoselective, leaving the imidoyl iodide intact as was unambiguously determined via X-ray crystallography. The broad display of reactivity led us to investigate the potential use of the spiroindolenine imidoyl iodides in the total synthesis of the Aspidosperma alkaloids. After numerous attempts, a strategy was developed using a C-2 prefunctionlized tryptamine-derived isocyanide prior to spirocyclisation. The dearomative spirocyclisation and diastereoselective reduction served as key steps in the total synthesis of 19-oxoaspidospermidine, which was achieved in 10 steps with an overall yield of 1.5% starting from tryptamine. The total synthesis highlights the applicability of the dearomative spirocyclisation and the potential to use tailored isocyanides in the synthesis of relatively complex natural products.