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Isocyanide-Based Multicomponent Reactions: Catalyst-Free Stereoselective Construction of Polycyclic Spiroindolines

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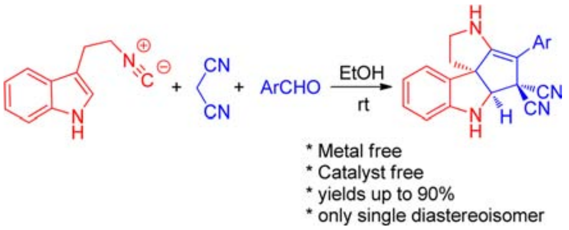
ABSTRACT



A novel catalyst-free one-pot tandem reaction for the stereoselective construction of polycyclic spiroindolines was developed. This method offers a straightforward access to structurally diverse polycyclic spiroindoline derivatives in high yields (up to 90%) with excellent levels of diastereoselectivity.

The development of efficient approaches to chemically and biologically important products from common starting materials, while combining economic and environmental aspects, has been an active topic in modern organic chemistry.[1,2] An increasing number of multicomponent reactions involving cascade processes have been reported, which provide powerful strategies for the total synthesis of natural products and synthetic building blocks.[3−5] In these reactions, multiple stereocenters could be generated with step economy, without further purification of various precursors, and tedious steps of protection and deprotection of functional groups.[6−8]

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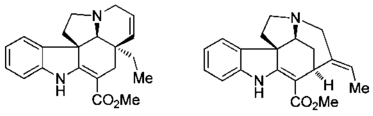
Polycyclic spiroindoline is a complex molecular skeleton that often exists in both natural products and pharmaceutical molecules with important biological activities.[9−12]

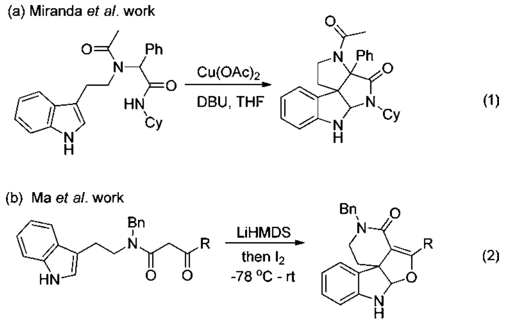


Tabersonine, **I** Akuammicine, **II**

Figure 1. Structures of polycyclic spiroindoline alkaloids.

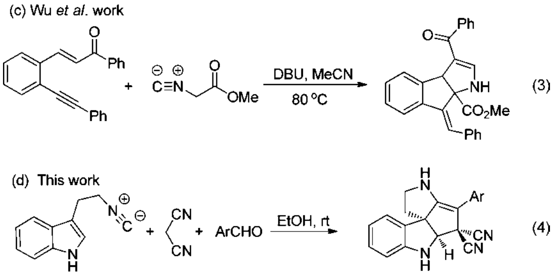
For example, tabersonine **I** and akuammicine **II** are characteristic members of the alkaloid family that continue to capture the imagination of organic chemists (Figure 1).[13−15] Polycyclic spiroindoline frameworks possessing quaternary carbon centers that assemble in a regio- and stereospecific manner from simple substrates have attracted attention over the past decades.

Scheme 1. Construction of Polycyclic Spiroindoline Skeletons



Recently, Van der Eycken et al.[16a] reported a post-Ugi Au-catalyzed domino cyclization method to generate spiroindolines. Miranda et al.[16b] reported that spiroindolines could be synthesized via a one-pot procedure combining an Ugi coupling and a copper-catalyzed oxidative process at a peptidyl position (Scheme 1, eq 1). Ma et al.[17] reported a protocol for assembling a polycyclic spiroindoline scaffold involving an intramolecular oxidative coupling of dianions derived from indole-embodied β-ketoamides using iodine as the oxidant, and the subsequent addition of the oxygen anion to the resultant imine moiety (Scheme 1, eq 2).

Scheme 2. Construction of Polycyclic Pyrrole Skeletons Based on Functionalized Isocyanide



Wu et al.[18] reported a base-promoted cascade reaction of (*E*)-2-alkynylphenylchalcone with 2-isocyanoacetate providing a novel and efficient route for the construction of tetrahydroindeno[2,1-*b*]pyrroles (Scheme 2, eq 3). They also developed a novel and efficient route for the construction of isoquinolines via a silver triflate catalyzed reaction of 2-alkynylbenzaldehyde with 2-isocyanoacetate.

Despite impressive advances in the construction of polycyclic spiroindolines, the most popular strategy for this transformation relies on transition-metal catalysts. These procedures have some drawbacks: the catalysts are expensive, high temperatures are required, and the reactions are characterized by low selectivity. Herein, we present a novel one-pot catalyst-free multicomponent reaction to construct polycyclic spiroindolines from simple and readily available 2-isocyanoethylindole,[19] aromatic aldehydes, and malononitrile. This transformation proceeds smoothly under mild conditions to afford the desired polycyclic spiroindolines in good to excellent yields with high diastereoselectivities (Scheme 2, eq 4).

We initiated our studies with the three-component reaction of 2-isocyanoethylindole **1a** (1 mmol), malononitrile **2a** (1 mmol), and 4-bromobenzaldehyde **3l** (1 mmol) in MeCN at room temperature for 5 h without any additive. To our delight, it afforded 4-bromophenyl-2,3,5a,6-tetrahydropyrrolo[3′,2′:2,3]cyclopenta[1,2-*b*]indole-5,5(1*H*)-dicarbonitrile **4l** in 90% LC-yield. The polycyclic spiroindoline **4l** was fully characterized by ^{1}H and ^{13}C NMR and IR spectra. Only a single diastereoisomer of polycyclic spiroindoline product **4l** was detected by NMR

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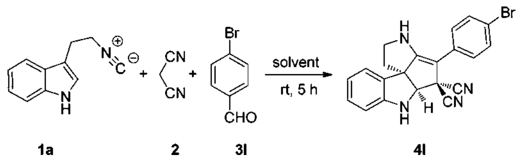
Table 1. Optimization of Reaction Conditions for the Multicomponent Reactions



entry	solvent	yield (%)[a]
1	MeOH	98
2	$CHCl_3$	87
3	MeCN	90
4	CH_2Cl_2	90
5	EtOH	99 (89[b])

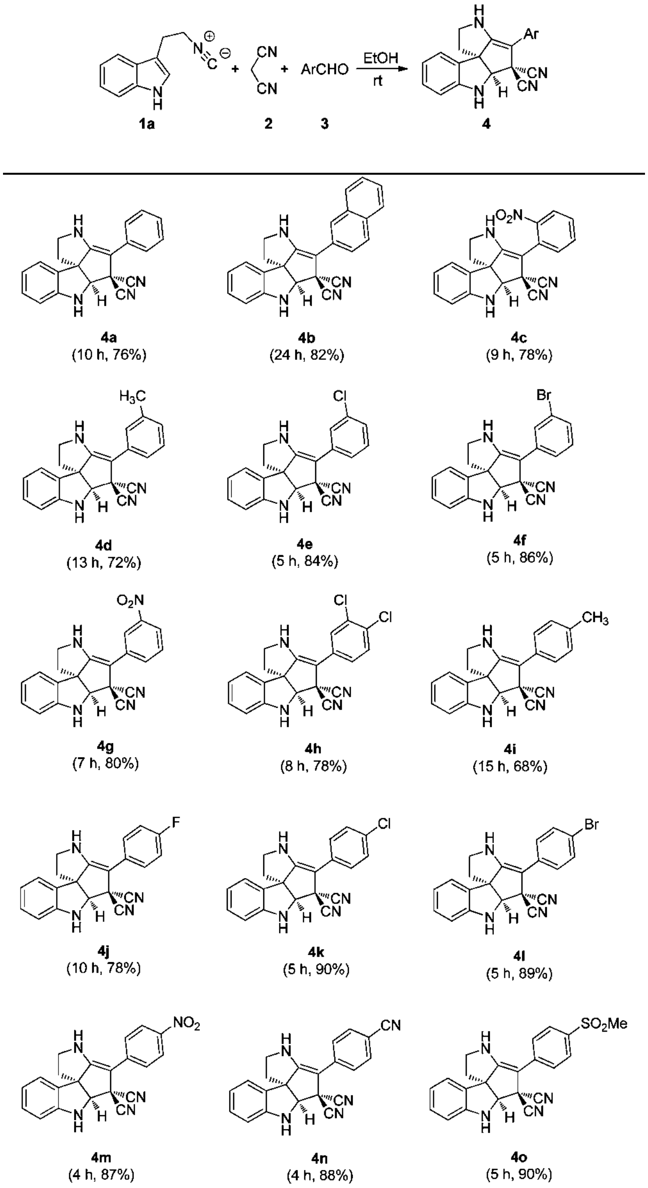
[a] The yields were determined by LC analysis using biphenyl as the internal standard. [b] Isolated yield.

analysis. To identify an ideal solvent for the transformation, the model reaction was investigated in different solvents. The results were summarized in Table 1. To our delight, the desired product **4l** could be obtained in good to excellent LC-yields in different solvents, and EtOH gave the best result. The desired product **4l** could be obtained in 89% isolated yield (Table 1, entry 5).

With the above optimized conditions in hand, the substrate scope was examined by using readily available starting materials. As presented in Scheme 3, 2-isocyanoethylindole **1a** with malononitrile **2** and various substituted aromatic aldehydes **3** worked well to afford he desired products (**4a** to **4o**) in moderate to excellent yields (72% to 90%) with high diastereoselectivities. Notably, polycyclic spiroindoline **4o** was obtained in excellent yield (90% yield) with **3o** bearing a strong electron-withdrawing group. When 3-methylbenzaldehyde **3d** bearing an electron-donating group was subjected to this reaction, the yield of the desired product **4d** was decreased to 72%. When other benzaldehyde derivates bearing F, CN, NO_2, Br, Cl groups were applied to the reaction, the desired products (**4j** to **4n**) could also be obtained in moderate to good yields. The structure of **4n** was further confirmed by single-crystal X-ray diffraction.

When 2-isocyanoethylindole derivatives **1b** to **1d** instead of **1a** was subjectd to the reaction with **2** and **3n** under the optimized conditions, the desired polycyclic spiroindoline derivatives **4p** to **4r** were obtained in 54% to 66% yield (Scheme 4, eq 5). Interestingly, when aliphatic pivalaldehyde was used instead of aromatic aldehydes, unrearranged product **8a** was obtained (Scheme 4, eq 6). However, other aliphatic aldehydes with α-H were employed in this reaction, and no corresponding polycyclic spiroindoline was obtained. When 2-(2-oxoindolin-3-ylidene) malononitrile was subjected to the reaction under the identical conditions, no polycyclic spiroindoline was observed (Scheme 4, eq 7). The possible reason is the steric hindrance of the 2-(2-oxoindolin-3-ylidene)malononitrile and the low polarity of the activated alkene.

Scheme 3. Reaction of 2-Isocyanoethylindole and Malononitrile with Aromatic Aldehydes



To better understand the mechanism of this reaction, we carried out the reaction of **1** with **5g** under the identical conditions. The desired product **4l** could also be obtained in similar yield (Scheme 4, eq 8).

Based on the above results, we proposed a plausible mechanism for this multicomponent reaction.[20] First, the reaction is initiated by Knoevenagel condensation of malononitrile **2** and the aldehyde **3** to perform the benzylidenemalonodinitrile **5**. Then, the isocyanide **1** undergoes nucleophilic addition to intermediate **6** followed by nucleophilic attack by the C3 of indole to afford intermediate **7**. Subsequently, intermediate **7** undergoes intramolecular nucleophilic addition to afford polycyclic spiroindoline derivatives **4** (Scheme 5).

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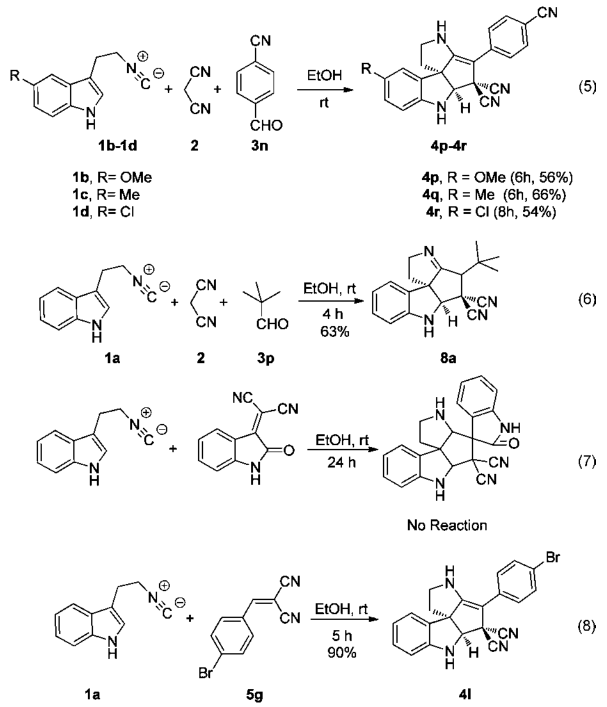
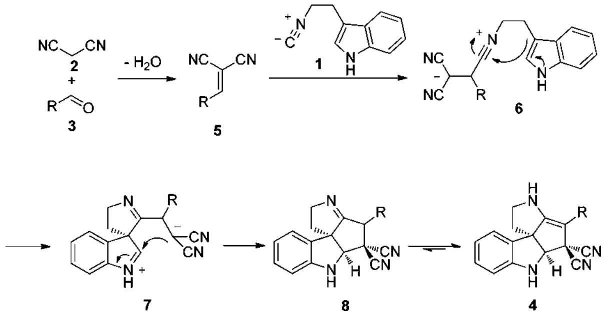
Scheme 4. Scope of the Construction of Polycyclic Spiroindolines



In conclusion, we have developed a novel catalyst-free multicomponent reaction for the construction of polycyclic spiroindolines by using 2-isocyanoethylindole with different types of aromatic aldehydes and malononitrile. The reactions proceed under mild conditions and performed the products in good to excellent yields with high diastereoselectivities. Further studies for the synthetic applications and synthesis of natural product analogs are ongoing in our laboratory.

Scheme 5. Proposed Mechanism for the Products **4**



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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds and X-ray crystallographic details of **4n** (CIF file; atomic coordinates, displacement parameters, bond lengths and angles, and torsion angles). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.