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Preparation of the Core Structure of *Aspidosperma* and *Strychnos* Alkaloids from Aryl Azides by a Cascade Radical Cyclization

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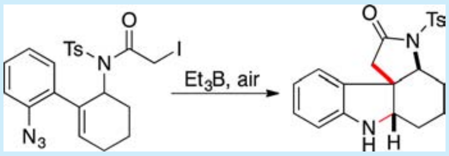
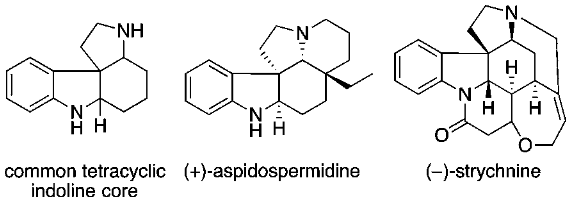
Supporting Information

ABSTRACT: A novel approach to prepare the core structure of *Aspidosperma* and *Strychnos* alkaloids is described. The strategy is based on a cyclization cascade involving the formation of quaternary carbon center followed by trapping of the radical intermediate by an aryl azide to build the 5-membered ring of the pyrrolocarbazole system. This reaction is run with triethylborane without the need for any hydrogen atom donor such as a tin hydride or tris(trimethylsilyl)silane, and it furnishes the tetracyclic framework as a single diastereomer. The influence of different *N*-protecting groups on the starting iodoacetamide has been examined.

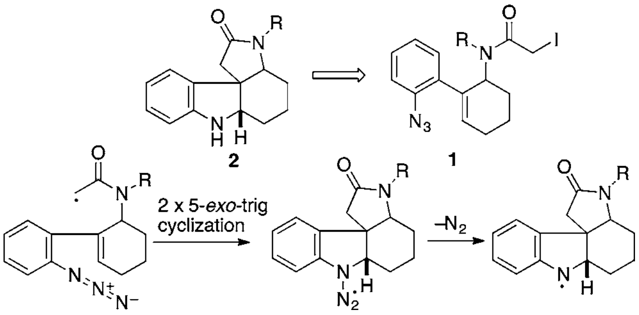


The *Aspidosperma* and *Strychnos* alkaloids are subfamilies of the monoterpene indole alkaloids, which represent the largest family of alkaloids with over 2000 members.[1] These complex natural products possess a broad range of chemical diversity and potent biological activity (e.g., anticancer, antimalarial, and antiarrhythmic).[1b] Structurally, many of these alkaloids share a common tetracyclic indoline core. This motif has long been a source of interest for chemists and a variety of inventive synthetic strategies have been developed toward its preparation.[2,3]



Radical chemistry proved to be a useful tool to access the tetracyclic core of *Aspidosperma* and *Strychnos* alkaloids.[4] Murphy and co-workers reported a formal synthesis of (±)-aspidospermidine that used an aryl radical triggered cascade cyclization to prepare the tetracyclic indoline framework from an aromatic iodide bearing an alkyl azide side chain.[5] Murphy's approach relied on the use of a highly reactive aryl radical generated from the corresponding iodide in the presence of a stoichiometric amount of tris(trimethylsilyl)silane.[6] Modifying the reaction sequence by starting with a stabilized α-amide radical and ending up with a cyclization onto an aryl azide would avoid the use of a hydrogen donor, such as a silane or a tin hydride, and potentially lead to better control of the cascade process. Moreover, aryl azides are known to be more stable and less prone to explosion than aliphatic azides.[7] Despite their promising reactivity profile, aromatic azides have rarely been used as radical traps.[8] Recently, we described a simple approach to prepare indolines, indoles, and benzopyrrolizidinones via a radical cascade reaction involving aryl azides as radical traps.[9] This radical cyclization process has been further applied to the preparation of more elaborate systems such as leucomitosanes.[10] Herein, we report a cascade cyclization reaction approach for the preparation of the tetracyclic core structure of *Aspidosperma* and *Strychnos* alkaloids according to the strategy depicted in Scheme 1. The tetracyclic indoline core **2** could be obtained from iodoacetamide **1** by two consecutive 5-*exo*-*trig* radical cyclizations.

Scheme 1. Synthetic Plan for the Tetracyclic Skeleton of *Aspidosperma* and *Strychnos* Alkaloids



In order to study the feasibility of the proposed retrosynthesis, preliminary experiments were run with two oxygenated analogues of **1** that were easily prepared from cyclohex-2-enol (see the Supporting Information). The iodoacetate **3** was investigated first using triethylborane in benzene at reflux under dilute conditions (0.05 M) (Scheme 2). Under these conditions, traces of the lactone **4** were identified by GC–MS analysis of the crude mixture, but it could not be isolated. The deiodinated acetate was the major product of the reaction. An attempt to run the reaction with tris(trimethylsilyl)silane and 2,2′-azobis(isobutyronitrile) (AIBN) as initiator gave

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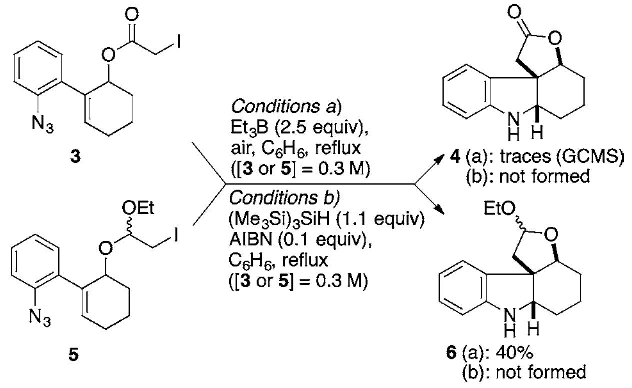
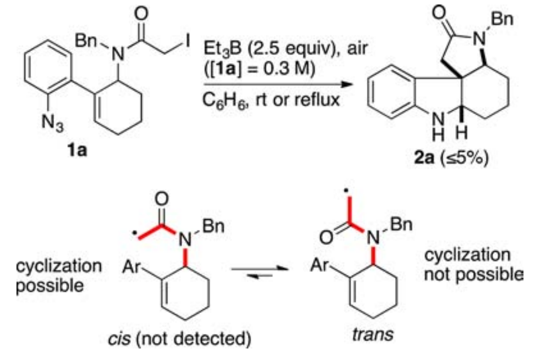
Scheme 2. Radical Cyclization of the Oxygenated Model Systems 3 and 6



exclusively the deiodinated acetate. Since formation of lactone from allyl iodoacetates is known to be a difficult process due to conformational effects,[11] we decided to employ the Ueno–Stork cyclization approach starting from the corresponding iodoacetal **5**.[12] Under the tris(trimethylsilyl)silane/AIBN conditions, only the deiodinated noncyclized acetal was formed. However, when the reaction was run with triethylborane/air according to the conditions we had developed for the leucomitosane synthesis,[10] the desired cyclized product **6** was obtained in moderate yield, demonstrating the feasibility of such a cascade process.

Cyclization of the benzylated iodoacetamide **1a** was investigated next. It was prepared in nine steps from commercially available cyclohex-2-enone (see the Supporting Information). Attempts to perform the radical cascade on **1a** using triethylborane in an open-to-air system at room temperature and refluxing benzene led only to traces amount of the indoline **2a** according to GC–MS analysis (Scheme 3).

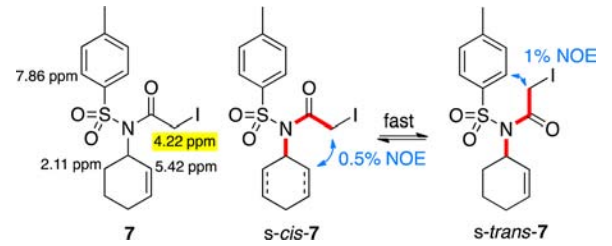
Scheme 3. Cyclization of the *N*-Benzylamide 1a and Conformation of the Carbamoylmethyl Radical



The failure of the cyclization leading to **2a** is directly linked to the conformation adopted by the unsymmetrically *N*,*N*-disubstituted carbamoylmethyl radical. Only the *cis*-conformer of the radical has a suitable geometry to undergo cyclization.[13] A ^{1}H and ^{13}C NMR NMR study of **1a** showed only one set of signals at room temperature, indicating that only one rotamer was present in the solution. NOE difference NMR experiments revealed that this rotamer possessed *trans* geometry (see the Supporting Information).

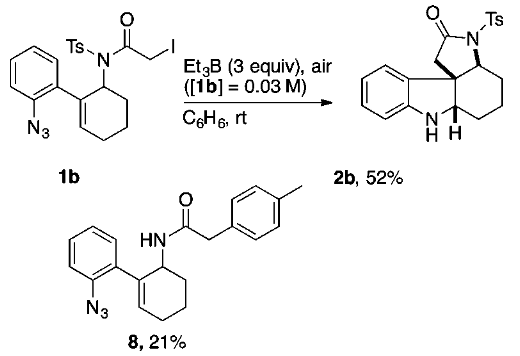
The relative stability of the two rotamers is influenced by steric effects.[14] Increasing the size of the amide protecting group should favor the desired *cis* conformer. However, this strategy was not further investigated since bulkier groups at nitrogen make the synthesis of the starting iodoacetamide awkward. Electronic effects can alter the rate of interconversion between two conformers. Nagashima[15] and Ikeda[16] reported independently that the use of electron-withdrawing substituents on the amide nitrogen atom, such as the *p*-toluenesulfonyl group, allows 5-*exo*-cyclization of sulfonamides onto double bonds in good yields, regardless of the reaction temperature. The presence of the desired rotamer was attributed to a lowering of the rotation barrier of the amide N–C(O) bond. This point was examined on substrate **7**, a compound that has been reported to undergo efficiently radical cyclization under iodine atom transfer conditions promoted by triethylborane.[16b] ^{1}H NMR study in CDCl$_3$ at variable temperatures showed between +50 and −30 °C only one set of sharp signals, indicating a rapid equilibration between the two conformations. At −50 °C, signals became broader, but only one set of coalescence signals was still observed. NOE difference spectra (irradiating the proton of the iodomethyl group at 4.19–4.26 ppm) confirmed the presence of both *s*-*cis* and *s*-*trans* amide conformers (Scheme 4). This short study confirmed that the electronic effects induced by the tosyl group provide essentially "free" rotation of the amide N–C(O) bond.

Scheme 4. NOE Difference Spectra in CDCl$_3$ (400 MHz) at Room Temperature for the *N*-Tosylated 7



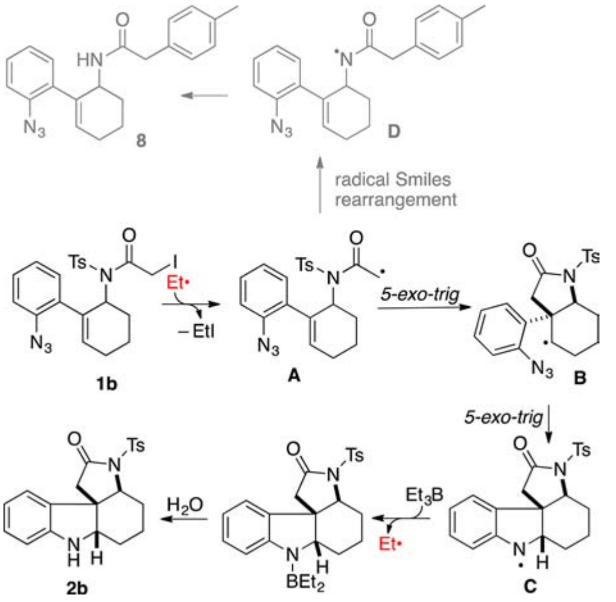
Therefore, the *N*-tosylated iodoacetamide **1b** was prepared in nine steps (23% overall yield) from cyclohexenone (see the Supporting Information). The radical cyclization was performed at room temperature using a 3-fold excess of triethylborane in an open-to-air system (Scheme 5). The tetracyclic core structure of **2b** was formed in 52% yield as a single diastereoisomer. A significant amount the side product **8** (21%) arising from a 1,4-aryl migration (radical Smiles

Scheme 5. Radical Cyclization of 1b Leading to the Tetracyclic Target Molecule



rearrangement)[17] was also detected (see Scheme 6 for the mechanism).

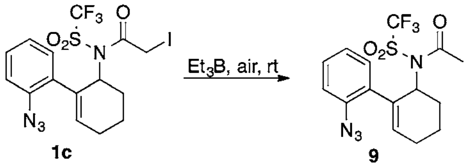
Scheme 6. Proposed Mechanism



A mechanism for the radical cyclization cascade is proposed in Scheme 6. In the presence of air (oxygen), triethylborane produces ethyl radicals that abstract an iodine atom from **1b** to generate the carbamoylmethyl radical **A**.[18] 5-*Exo-trig* cyclization of radical **A** afforded the secondary radical **B** that reacts with the aryl azide via a second 5-*exo-trig* cyclization followed by a rapid loss of N_2 to afford the aminyl radical **C**. Radical **C** sustains the radical chain by reacting with triethylborane. Finally, hydrolysis of the aminoborane provides **1b**. In this set of reactions, Et_3B acts both as a radical initiator and a chain-transfer reagent.[19] The intermediate **D** responsible for the formation of the side product **8** is depicted on top of Scheme 6. The *N*-tosylcarbamoylmethyl radical **A** undergoes a radical Smiles rearrangement leading to **D**. Interestingly, this side reaction is also a chain process. The triethylborane method could become an efficient and simple way to arylate α-amide radicals since it does not involve the use of any hydrogen atom donor that could trap the initial radical.

Finally, in order to avoid the Smiles rearrangement, the use of *N*-methanesulfonyl iodoacetamide and *N*-trifluororomethanesulfonyl **1c** was envisaged. The synthesis of the *N*-methanesulfonyl derivative according to the method used for **1b** failed at the *N*-acylation stage. The *N*-trifluoromethanesulfonyl amide **1c** could be synthesized. However, all attempts to run cyclization with **1c** led to a clean formation of the deiodinated acetamide **9** (Scheme 7). The strong electron-withdrawing character of the trifluoromethanesulfonyl group presumably favors an ionic deiodination pathway.[13]

Scheme 7. Cyclization Attempt of the *N*-Trifluoromehtanesulfonyl Derivative 1c



In conclusion, we have developed a mild and diastereoselective radical cyclization cascade involving an aryl azide as a final radical trap to prepare the tetracyclic core of *Strychnos* and *Aspidosperma* alkaloids **2b**. This reaction does not require the use of a hydrogen donor source since triethyborane, used in stoichiometric amounts, is acting as a chain-transfer reagent, and hydrolysis during the workup procedure affords the desired indoline skeleton. This approach is particularly suitable to run cascade reaction reactions involving one (or more) slow radical reactions. The tetracyclic structure **2b** has been prepared in 10 steps and 12% overall yield from cyclohex-2-enone. This study highlights also the importance of *N*-protecting groups in radical cyclization involving amides.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00306.

> Experimental procedures, full characterization of new products, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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