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An Aza-Prins Cyclization Approach to Functionalized Indolizidines from 2-Allylpyrrolidines

Xiaoxi Liu, Michael P. McCormack, and Stephen P. Waters*

Department of Chemistry, The University of Vermont, 82 University Place, Burlington, Vermont 05405, United States

Stephen.Waters@uvm.edu

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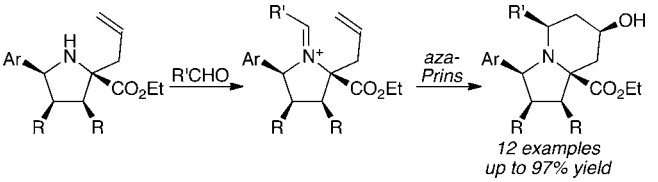
ABSTRACT



The stereoselective synthesis of a diverse set of functionalized indolizidine systems has been accomplished through the aza-Prins cyclization of 2-allylpyrrolidines. The condensation of aldehydes onto 2-allylpyrrolidines yields iminium ions that undergo highly diastereoselective aza-Prins cyclization, producing up to two stereogenic centers and two new rings in one step.

The indolizidine scaffold is prevalent in a variety of structurally complex, biologically active natural products.[1] Examples of such alkaloids include castanospermine (**1**, Figure 1) and swainsonine (**2**), known for their ability to inhibit glycosidase.[2] The *Securinega* indolizidine alkaloids securinine (**3**) and phyllanthine (**4**) have been shown to possess antitumor, antimalarial, antibacterial properties[3] as well as central nervous system activity as GABA receptor antagonists.[4] The therapeutic potential of these alkaloids has prompted organic chemists to investigate more concise and stereoselective methods for their construction.[5]

Our laboratory has developed a domino 2-aza-Cope-[3 + 2]-dipolar cycloaddition protocol for the preparation

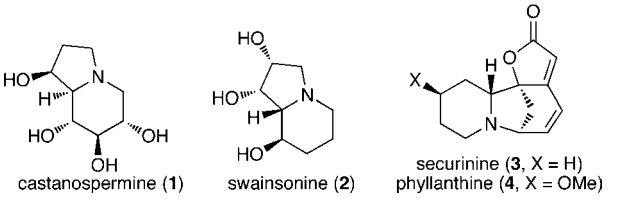


Figure 1. Biologicaly active indolizidine natural products.

of functionalized 2-allylpyrrolidine rings (Scheme 1).[6] In this sequence, the condensation of a homoallylic amine (cf. **5**, Scheme 1) with ethyl glyoxylate affords an imine of type **I**, which after facile 2-aza-Cope rearrangement delivers an azomethine ylide precursor of type **II**. Addition of AgOAc and Et_3N furnishes a stabilized, *N*-metalated azomethine ylide, which in the presence of a dipolarophile (**6**) undergoes subsequent [3 + 2] dipolar cycloaddition to afford a highly substituted 2-allylpyrrolidine (**7**) in a one-pot process. Up to four stereogenic centers are created within the proline cycloadduct, and the resultant 2-allyl moiety presents a convenient point for additional structural

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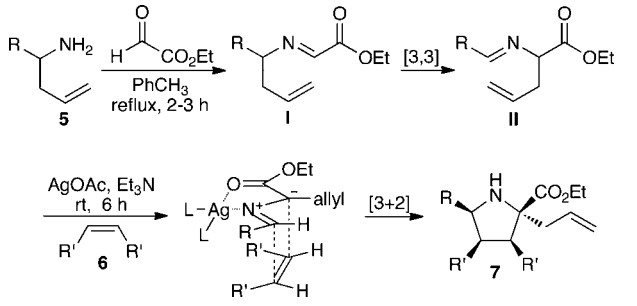
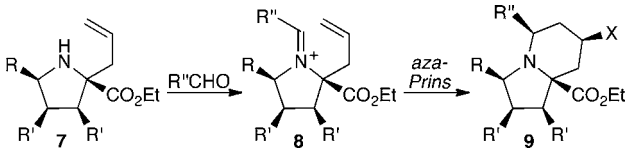
advancements. We are currently investigating the synthetic versatility of the pyrrolidine nitrogen and allylic functions in pyrrolidine **7** as functional points for additional ring-forming events, thereby allowing synthetic chemists to expand the range of *N*-heterocyclic systems obtainable through our method. Herein, we report the outcomes of our studies, which have enabled a novel route to indolizidine ring systems through the aza-Prins cyclization.

Scheme 1. 2-Aza-Cope-[3 + 2] Dipolar Cycloaddition Route to Functionalized 2-Allylpyrrolidines



The aza-Prins cyclization has most often been employed as a method to construct piperidine ring systems[7] and is gaining attention as a tactic in the synthesis of piperidine-containing natural products.[8] However, while applications of the aza-Prins cyclization to give piperidines through iminium[9] and acyliminium[10] ion ring closures are well-documented, synthetic applications toward the indolizidine ring system are much less developed.[11] Although 2-allylpyrrolidine precursors have been used to prepare indolizidines through ring-closing metathesis[12] and nitrone cycloaddition[13] strategies, far fewer examples of their use in aza-Prins or related cationic π-cyclizations have been reported.[14] Drawing upon our ability to access a variety of 2-allylpyrrolidine scaffolds through the 2-aza-Cope-[3 + 2]-dipolar cycloaddition sequence, we wished to explore the feasibility of preparing indolizidines through the aza-Prins cyclization. Condensation of an aldehyde onto the pyrrolidine nitrogen of **7** (Scheme 2) would furnish an iminium ion (**8**), which could undergo nucleophilic attack by the pendant allyl group. Interception of the developing carbocation by either the solvent or a tethered nucleophile would furnish the six-membered ring of the indolizidine (**9**) and two additional stereocenters. In this manner, the use of tandem, multicomponent reactions would provide access to functionalized indolizidines in a concise and stereoselective fashion.[15]

Scheme 2. Synthesis of Indolizidines through Aza-Prins Cyclization of 2-Allylpyrrolidines



In the early planning stages, we anticipated that the condensation of an aldehyde onto an already sterically encumbered, neopentyl pyrrolidine nitrogen might present a challenge to our synthetic approach. For our initial studies, formaldehyde was chosen as the electrophilic component. Gratifyingly, treatment of 2-allylpyrrolidine **10a** (Scheme 3) with aqueous formaldehyde (10 equiv) and TFA (1.0 equiv) in wet acetonitrile for 24 h at ambient temperature provided indolizidine **11a** in 80% yield as a single observable diastereomer. Aza-Prins cyclizations of 2-allylpyrrolidines **10b** and **10c** under similar conditions gave indolizidines **11b** and **11c** as single diastereomers in 79 and 82% yields, respectively. Conducting these processes in aqueous media promoted clean termination of the aza-Prins reaction through nucleophilic attack by water, affording hydroxy-substituted indolizidines in good overall yields. The high level of diastereoselectivity observed in this cyclization may be attributed to a chair transition state in which the pyrrolidine ring fusions occupy equatorial positions with respect to the newly forming piperidine ring, as well as axial approach of the incoming nucleophile (water) in a favorable antiperiplanar alignment with the π^* orbital of the iminium ion. These stereochemical assignments were confirmed through 2D NMR spectrocopy as well as NOE enhancement studies.

Encouraged by these findings, additional aldehyde components were surveyed. Glyoxylic acid, in the absence of TFA, readily underwent condensation at rt onto the

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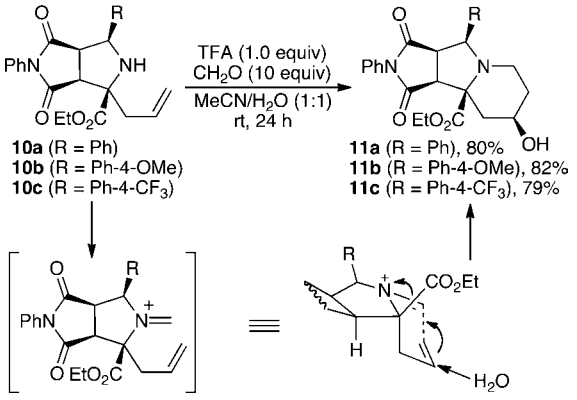
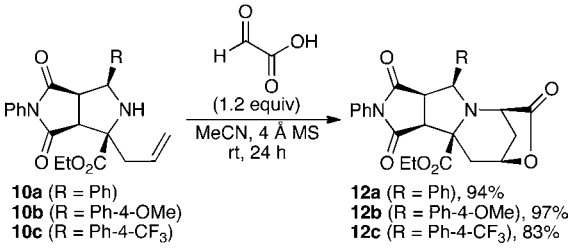
Scheme 3. Aza-Prins Cyclizations of 2-Allylpyrrolidines with Formaldehyde



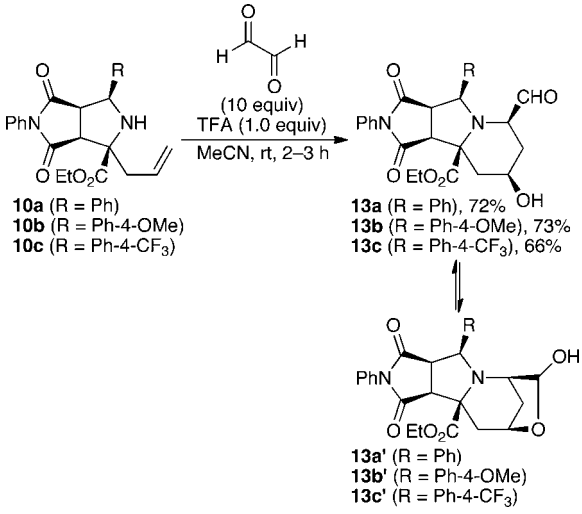
pyrrolidine nitrogen of **10a** (Scheme 4). After olefin–iminium ion cyclization, lactone **12a** emerged within 24 h in 94% yield as one diastereomer. The formation of lactone **12a** may be rationalized by ring closure of the olefin in **10a** onto the iminium ion followed by nucleophilic interception of the resulting carbocation by the carboxyl group in glyoxylic acid.[16] In like manner, the reactions of 2-allylpyrrolidines **10b** and **10c** under similar conditions gave indolizidine lactones **12b** and **12c** in good yields (97 and 83%, respectively) as single diastereomers. Spectroscopic analysis of indolizidine **12a** revealed that the newly formed lactone ring in **12a** adopts a *syn*-1,3-diaxial conformation with respect to the indolizidine system. These observations were later confirmed through X-ray analysis and chemical correlation to a related compound, **13c′** (vide infra). Overall, the use of glyoxylic acid as the aldehyde component led to the formation of two additional rings and two new stereogenic centers in a single step.

Scheme 4. Aza-Prins Cyclizations of 2-Allylpyrrolidines with Glyoxylic Acid



The use of glyoxal as the aldehyde component led to the formation of both indolizidine and lactol ring systems. Treatment of 2-allylpyrrolidines **10a**–**c** with aqueous glyoxal (10 equiv) and TFA (1.0 equiv) effected complete aza-Prins cyclization within 2–3 h at rt to afford indolizidine products **13a**–**c** in 66–73% yield (Scheme 5). These indolizidines were observed to exist in solution as equilibrating mixtures of their corresponding hydroxy-aldehyde (major) and lactol (minor) forms. In $CDCl_3$, the hydroxy-aldehyde forms were predominate in ratios between 2:1 and 7:1 as measured by integration of their ^1H NMR spectra.

Scheme 5. Aza-Prins Cyclizations of 2-Allylpyrrolidines with Glyoxal



Recrystallization of **13c** from MeOH:H_2O (3:2) gave colorless prisms, which were revealed by X-ray analysis to be the lactol form (**13c′**, Figure 2). The X-ray crystal structure of **13c′** confirmed that the newly formed six-membered ring of the indolizidine adopts a chairlike conformation, while the two new stereocenters of the lactol function assume a *syn*-1,3-diaxial relationship.

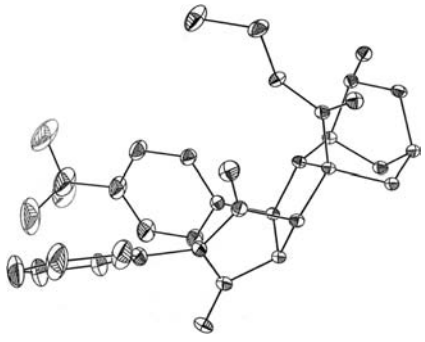


Figure 2. X-ray crystal structure of lactol **13c′**.

Aza-Prins cyclizations using ethyl glyoxylate (Scheme 6) required somewhat more forcing conditions, presumably due to the increased steric encumbrance of the aldehyde component. A variety of reaction parameters were investigated with 2-allylpyrrolidines **10a**–**c** to identify the optimal conditions. Good conversions to the corresponding indolizidines were best achieved by conducting the

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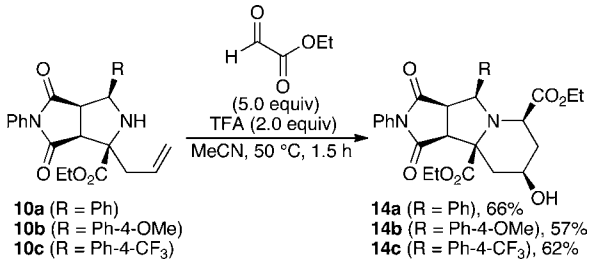
Scheme 6. Aza-Prins Cyclizations of 2-Allylpyrrolidines with Ethyl Glyoxylate



reactions at 50 °C, as aza-Prins cyclizations were not observed at room temperature. In this manner, treatment of **10a** with ethyl glyoxylate (5.0 equiv) and TFA (2.0 equiv) for 1.5 h delivered indolizidine **14a**, bearing two ester and one alcohol function, in 66% yield. Although this increase in temperature allowed for shorter reaction times, prolonged exposure of the hydroxy-esters **14a**–**c** to the reactions conditions for more extended times (3–5 h) led to the gradual formation of lactones **12a**–**c**, presumably through acid-catalyzed, intramolecular transesterification. Therefore, prompt neutralization after consumption of **10a**–**c** was necessary for good conversions to **14a**–**c**. That the indolizidines **14a**–**c** could be transformed to **12a**–**c** through lactonization indicated a stereochemical correlation between the two systems. Similar to the aza-Prins cyclizations with previous aldehydes, the resulting new stereogenic centers of the indolizidine ring adopt a *syn*-1,3-diaxial relationship.

In summary, we have developed a new and operationally facile method for the synthesis of indolizidines though aza-Prins cyclizations of 2-allylpyrrolidines. Though aza-Prins cyclizations have proven to be effective for the preparation of piperidines, our work now expands the scope of this reaction to include indolizidine scaffolds. We have also demonstrated that 2-allylpyrrolidines, now readily accessible through our domino 2-aza-Cope-[3 + 2]-dipolar cycloaddition sequence, are useful precursors for the preparation of additional heterocyclic systems. Synthetic applications of the aza-Prins cyclization toward alkaloid natural products bearing indolizidine frameworks are now being investigated.

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Supporting Information Available. Experimental procedures, characterization data, and NMR spectra for all new compounds. X-ray crystallographic information for compound **13c′** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.