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Synthesis of Fused Tricyclic Amines from Enolizable Acyclic Aldehydes by Cyclization then Dipolar Cycloaddition Cascade: Synthesis of Myrioxazine A

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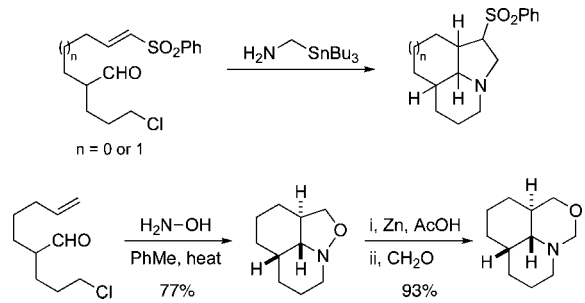
ABSTRACT



A tandem one-pot reaction involving a condensation, then cyclization (*N*-alkylation), followed by an azomethine ylide or nitrone dipolar cycloaddition allows a synthesis of tricyclic amines from acyclic enolizable aldehydes. The reaction was unsuccessful using amino acids or esters but was successful with (tributylstannyl)methylamine or hydroxylamine. One of the products was converted in two steps to the alkaloid (±)-myrioxazine A. The chemistry also provides a formal synthesis of the antimalarial alkaloids myrionidine and schoberine.

Reactions where multiple bonds are formed in one sequence without isolating intermediates, changing the reaction conditions or adding reagents, represent efficient and economic processes.[1] Multiple bond forming reactions, or multicomponent reactions, are often termed cascade, tandem, or domino reactions and can be used for the formation of complex products.[2] For example, the formation of a 1,3-dipole followed by an in situ intramolecular cycloaddition represents a powerful way of accessing bicyclic compounds.[3] In addition, such processes generally offer high levels of regio- and stereocontrol. Cascade reactions where three rings can be formed in one reaction are particularly efficient and

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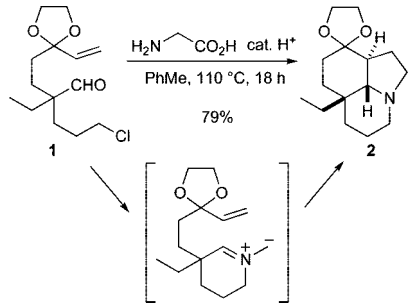
allow rapid access to structural and stereochemical complexity. One such cascade class involves a cyclization to form a dipole which can then undergo an intramolecular cycloaddition. This strategy has been used for the synthesis of polycyclic oxygen-containing products, where cyclic carbonyl ylides (often generated by the reaction of a carbenoid with an intramolecular carbonyl group) undergo a cycloaddition with an internal dipolarophile.[4] In a similar way, an intramolecular 1,3-dipolar cycloaddition reaction of a nitrone ylide with a dipolarophile can lead to a range of polycyclic compounds.[5] Another class of cascades, again forming multiple rings in one reaction, involves tandem [4 + 2]/[3 + 2] cycloadditions of either 1,3,4-oxadiazoles (coupled with nitrogen extrusion)[6] or nitroalkenes.[7]

Our cascade strategy relies on the ability to form an azomethine or nitrone ylide from an aldehyde and a primary amine (e.g., glycine, glycine ethyl ester, or hydroxylamine) using an in situ N-alkylation.[8] In our recent synthesis of three *Aspidosperma* alkaloids, we demonstrated such a process using aldehyde **1**, where treatment with glycine generates a cyclic azomethine ylide which then undergoes an intramolecular cycloaddition on the tethered alkene, to give amine **2** (Scheme 1).[9]

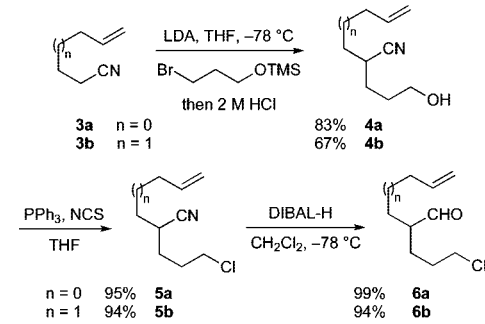
Scheme 1. Synthesis of Tricyclic Amine **2** Using a Cyclization/Cycloaddition Cascade



A number of possible tricyclic amine targets lack the ring junction ethyl group. Thus, to use the cascade chemistry as a general method for total synthesis, the use of enolizable aldehydes must be evaluated. We report here our results with such aldehydes.

Deprotonation of 5-hexenenitrile (**3a**) or 6-heptenenitrile (**3b**) with LDA and alkylation with 1-bromo-3-chloropropane led to inseparable mixtures of mono- and dialkylated products. To circumvent this problem, the trimethylsilyl ether of 3-bromopropan-1-ol was used as the alkylating agent. Following an acidic workup, the alcohols **4a** and **4b** could be separated easily from the dialkylated diol products (Scheme 2). Subsequent chlorination of the alcohols with

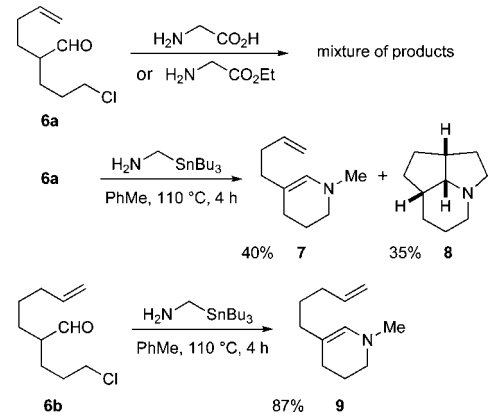
Scheme 2. Synthesis of Aldehydes **6**



PPh_3 and *N*-chlorosuccinimide (NCS), then reduction with DIBAL-H, gave the aldehydes **6a** and **6b**.

Treatment of aldehydes **6a** and **6b** with glycine or glycine ethyl ester (to form the unstabilized or stabilized ylides, respectively) gave an inseparable mixture of products (in each case, NMR spectroscopy showed the presence of alkene in the mixture) (Scheme 3). The failure of this chemistry

Scheme 3. Treatment of Aldehydes **6** with Amines



contrasts with that of the analogous nonenolizable substrates.[9] As an alternative to the use of glycine or glycine ethyl ester, it is sometimes possible to generate azomethine ylides from enolizable aldehydes via their imines then desilylation or, preferably, destannylation, which is thought to be faster than

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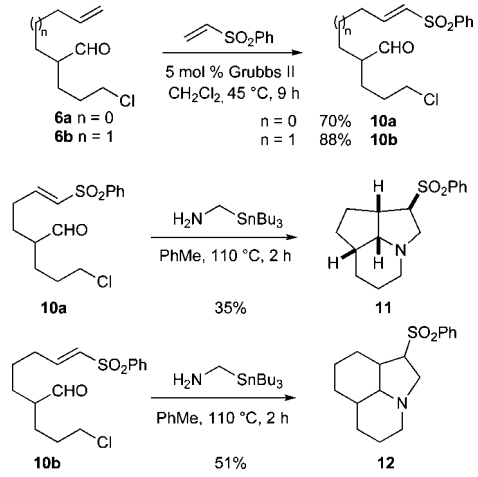
enamine formation.[8a,10,11] Pearson and co-workers have found that azomethine ylides can be generated readily from *N*-(tri-*n*-butylstannyl)methyl iminium salts without the need for an additive (such as fluoride) to initiate demetalation.[8a]

Following this procedure, we were pleased to find that treatment of aldehyde **6a** with (tri-*n*-butylstannyl)methylamine gave tricyclic amine **8** as a single isomer (Scheme 3). The all *cis* configuration was confirmed by ^{1}H NMR spectroscopy. In addition to amine **8**, enamine **7** was also isolated, arising either from deprotonation of the iminium salt followed by destannylation and protonation or by tautomerization of the azomethine ylide after destannylation. In the case of aldehyde **6b**, the cycloaddition to form a new six-membered ring must be slower than that to form a five-membered ring, and as such, only the analogous enamine **9** was isolated (Scheme 3).

In attempts to increase the rate of cycloaddition relative to the rate of enamine formation, aldehydes **10a** and **10b** were prepared by cross metathesis with phenyl vinyl sulfone catalyzed by Grubbs' second-generation catalyst (Scheme 4). However, activation of the dipolarophile in aldehyde **10a**

Scheme 4. Cross Metathesis and Subsequent Cyclization/Cycloaddition



failed to give an increase in yield of the desired tricyclic amine (**11**), which we ascribe to the inherent instability of the aldehyde **10a**.

In the case of aldehyde **10b**, activation of the dipolarophile facilitated the desired cycloaddition, and three tricyclic amines with structure **12** were obtained in moderate yield (dr 1:1:1) with no observable enamine product. The structures of two of these cycloadducts (**12b** and **12c**, Figure 1) were

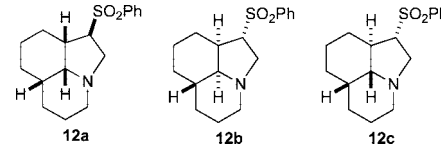
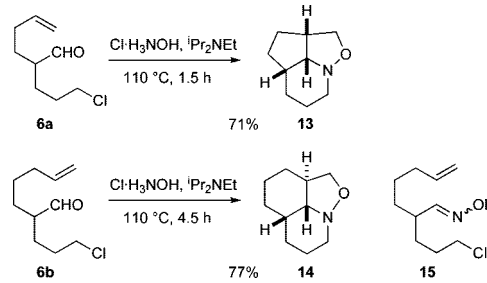


Figure 1. Structures of the products **12**.

elucidated by single-crystal X-ray analysis and the third isomer (**12a**) by ^{1}H NMR spectroscopy. In similar studies with nonenolizable aldehydes (using a substrate similar to **10** but with an ethyl group rather than a hydrogen atom α- to the aldehyde), only products with stereochemistry analogous to **12a** and **12c** were obtained.[9a] It therefore seems that the *trans*-decalin moiety in product **12b** can arise when using an enolizable aldehyde.

In contrast to azomethine ylides, dipolar cycloaddition of nitrone ylides derived from enolizable aldehydes is common, and we were pleased to find that treatment of the aldehyde **6a** with hydroxylamine gave the cycloadduct **13** in good yield (Scheme 5). Similarly, treating aldehyde **6b** with hydroxylamine gave the cycloadduct **14** (together with some oxime **15**, which could be converted to **14** on further heating). The stereochemistry of the cycloadducts was confirmed by ^{1}H NMR spectroscopy.

Scheme 5. Cyclization/Cycloaddition Using Hydroxylamine



The N−O bond in cycloadduct **14** was cleaved by reaction with zinc in acetic acid to give the amino alcohol **16** (Scheme 6). This amino alcohol was heated with paraformaldehyde under acid catalysis to complete the total synthesis of (±)-myrioxazine A, a natural product isolated from *Myrioneuron nutans*.[12] The synthesis of the amino alcohol **16** also

(7) For some recent examples, see: (a) Denmark, S. E.; Baiazitov, R. Y. *J. Org. Chem.* **2006**, *71*, 593. (b) Denmark, S. E.; Gomez, L. *J. Org. Chem.* **2003**, *68*, 8015. (c) Denmark, S. E.; Juhl, M. *Helv. Chim. Acta* **2002**, *85*, 3712. (d) Denmark, S. E.; Cottell, J. J. *J. Org. Chem.* **2001**, *66*, 4276.

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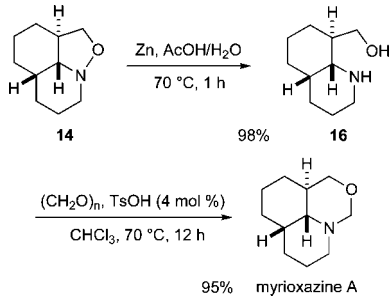
(13) Pham, V. C.; Jossang, A.; Grellier, P.; Sévenet, T.; Nguyen, V. H.; Bodo, B. *J. Org. Chem.* **2008**, *73*, 7565.

Scheme 6. Synthesis of Myrioxazine A from Cycloadduct **14**



completes a formal synthesis of the antimalarial alkaloids myrionidine and schoberine.[13]

In summary, the method described here allows the formation of tricyclic amines from acyclic enolizable aldehydes, using a condensation/cyclization/cycloaddition cascade. As such, the methodology may find application in the total synthesis of nitrogen-containing heterocyclic compounds bearing ring junction protons. This is demonstrated by an expedient synthesis of (±)-myrioxazine A in six steps and 42% overall yield, starting from 6-heptenenitrile.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of NMR spectra for the products **4**−**14**, **16**, and myrioxazine A and X-ray structures for **12b** (CCDC-714564) and **12c** (CCDC-714563). This material is available free of charge via the Internet at http://pubs.acs.org.

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