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# Synthesis of tetracyclic indole-containing ring systems by intramolecular cycloadditions of azomethine ylides

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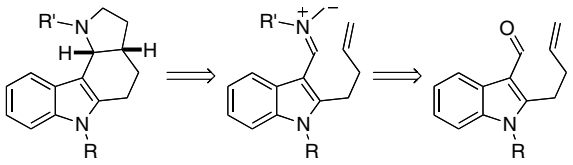
**Abstract**—Dipolar cycloaddition of azomethine ylides derived from addition of amines to a 2-butenylindole-3-carboxaldehyde provides a stereoselective synthesis of tetracyclic products present in a variety of indole alkaloids. The chemistry was applied to a formal synthesis of the *iboga* alkaloid deethylibophyllidine.


Dipolar cycloaddition reactions are one of the most important methods to access five-membered heterocyclic ring systems.[1] The use of azomethine ylide dipoles leads to pyrrolidines, an important ring system present in a great number of natural products. When the dipole and dipolarophile are placed within the same molecule, then intramolecular cycloaddition provides bicyclic (or polycyclic) products.[2] In such cases (in contrast to intermolecular reactions), terminal alkenes that are unactivated (no electron-withdrawing group) can often be used as the dipolarophile.

Our interest in the use of this chemistry for the synthesis of the core ring system of alkaloids such as manzamine A,[3] led us to attempt dipolar cycloaddition reactions on ylides such as **2** (Scheme 1). Such azomethine ylides should be accessible by condensation of amines with aldehyde **3**. This letter reports the successful cycloaddition of ylide dipoles **2** onto the tethered terminal alkene unit to give the tetracyclic products **1**.




**Scheme 1.** Disconnection of a tetracyclic indole ring system.

The tetracyclic ring system shown in compound **1** is found in several indole alkaloids of the *iboga* family. For example, the alkaloid deethylibophyllidine **4** (Fig. 1) forms part of this family.[4] There are several syntheses of this compound,[5] one of which uses amine **5**, itself prepared in six steps from *O*-methyltyramine.[5c] We demonstrate here a short stereoselective synthesis of amine **5** and hence a formal synthesis of the alkaloid deethylibophyllidine.

Aldehyde **3** in which the indole nitrogen atom is protected as a methyl carbamate (i.e., compound **9**) was selected as the substrate needed to test the key dipolar cycloaddition reaction. This compound was prepared in three steps from 2-methylindole (**6**) as shown in Scheme 2.

This chemistry makes use of the known deprotonation (and methylation) of 2-methylindole (**6**) using excess

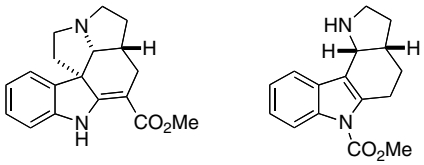



**Figure 1.** Deethylibophyllidine **4** and a precursor **5**.

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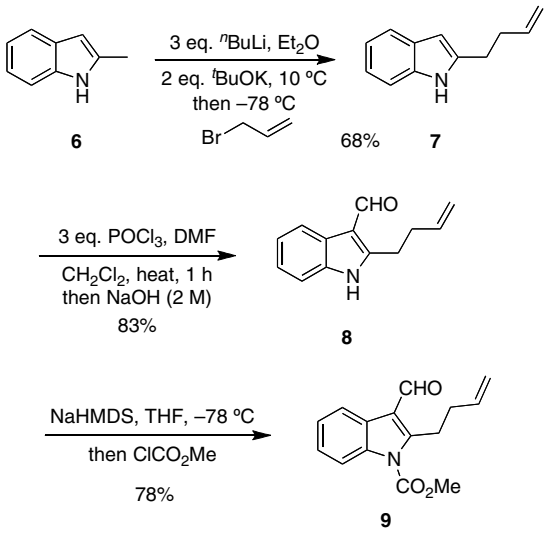
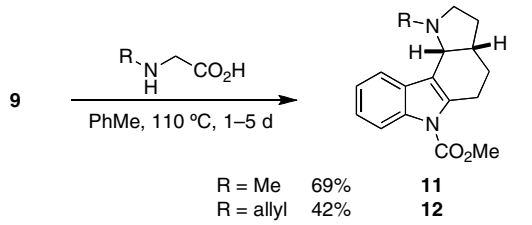
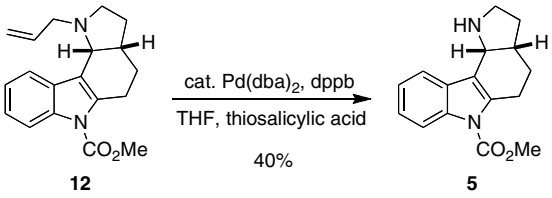



**Scheme 2.** Preparation of the aldehyde **9**.




**Scheme 4.** Cycloaddition with *N*-methyl and *N*-allyl glycine.

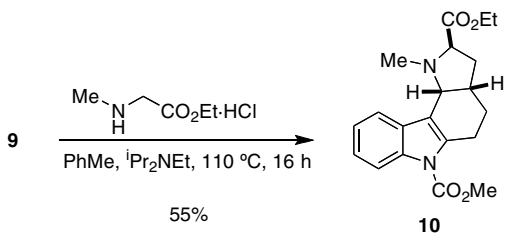



**Scheme 5.** Deallylation to give tetracycle **5**.

*n*-butyllithium and potassium *tert*-butoxide (followed by addition of iodomethane).[6] Addition of allyl bromide to the dianion provided the desired 2-but-3-enylindole **7** in reasonable yield. Product **7** was subjected to standard Vilsmeier formylation conditions to give aldehyde **8**. Protection of the indole nitrogen atom with methyl chloroformate under basic conditions gave the desired substrate **9**.

There is a report in the literature of the formation of azomethine ylides from *N*-alkyl-2-aryl-indole-3-carboxaldehydes.[7] In this case, a subsequent 1,7-electrocyclic reaction occurs with the 2-aryl substituent. In our substrate **9**, we have an alkenyl group located appropriately for cycloaddition. We were pleased to find that heating aldehyde **9** with the hydrochloride salt of *N*-methyl glycine ethyl ester (sarcosine ethyl ester) in toluene and diisopropylethylamine resulted in the formation of cycloadduct **10** (Scheme 3). The best yields were obtained using an excess (4 molar equiv) of *N*-methyl glycine ethyl ester and diisopropylethylamine. The $^{1}$H NMR spectrum of the product showed one major product with only a small amount of a minor, inseparable stereoisomer. The relative stereochemistry of the major product is shown in structure **10** and was confirmed by NOE spectroscopy. This stereochemistry equates to cycloaddition through an ylide with S-shaped geometry, which is in line with the cycloadditions of related substrates.[2]

Cycloaddition of aldehyde **9** was also attempted with *N*-methyl glycine and with *N*-allyl glycine and resulted in the formation of the tetracyclic products **11** and **12** (Scheme 4). In this chemistry, the ylide dipole forms after decarboxylation.[8] Only the cis-fused ring junction stereoisomer was formed in each case.




**Scheme 3.** Cycloaddition with sarcosine ethyl ester.

With the successful cycloaddition to give adduct **12**, we investigated its N-deallylation. We were pleased to find that using palladium catalysis, the allyl group was removed to give product **5** (Scheme 5). The spectroscopic data of product **5** matched that reported in the literature.[5c] As this compound has been converted (in four steps) to deethylibophyllidine, we have achieved a short, stereoselective formal synthesis of this alkaloid.

In summary, we have demonstrated that aldehyde **9** can be used to generate azomethine ylides that undergo intramolecular cycloaddition on to the pendent alkene group. The chemistry provides an efficient and stereoselective synthesis of tetracyclic compounds and was applied to a formal synthesis of the alkaloid deethylibophyllidine.

## References and notes

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