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A New Intramolecular Aryne Cycloaddition Approach to Lycorines

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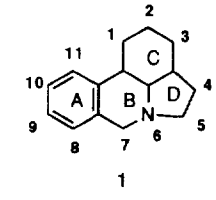
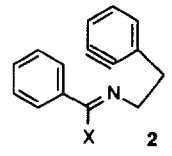
Abstract: A new approach to lycorines based on the intramolecular cycloaddition of an azadiene and an aryne is reported. The azadiene component was formed by the double bond of an imine and a double bond belonging to an aromatic ring, and the aryne was generated by dehydrohalogenation of an aryl bromide with LDA.

The lycorine alkaloids are a group of compounds characterized by the skeleton **1** and isolated from Amaryllidaceae plants.[1] This group has attracted the attention of chemists and pharmacologists due to the interesting properties of some of its members. For example, hippadine inhibits fertility in mice;[2] anhydrolycorinium chloride shows activity against P-388 leukemia;[3] and ungeremine is active against several types of tumour.[4]

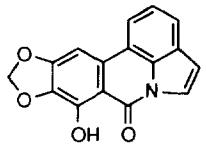
In recent years we have developed a new strategy for the synthesis of lycorines based on the intramolecular cycloaddition of an azadiene and an aryne.[5] As the azadiene component we have hitherto used an imidate (**2** ; X=-O$^-$) generated by treatment of the corresponding secondary amide with LDA. We now report preliminary results obtained with an alternative procedure based on the use of an imine (**2**; X=H) as azadiene.



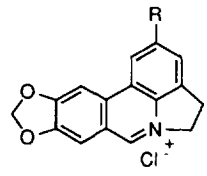
1



2



Hippadine



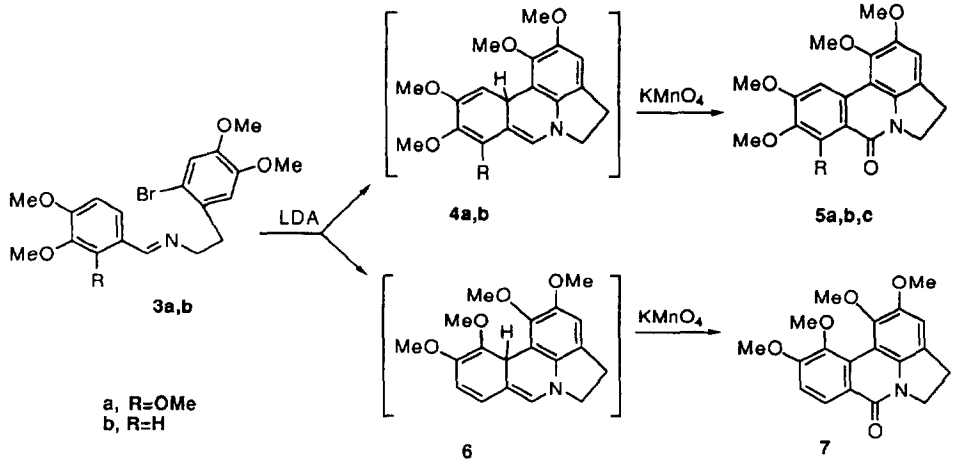
R=H, Anhydrolycorinium chlorid

R=OH, Ungeremine

Figure 1

Imines **3a** and **3b** were obtained by condensation of the corresponding aldehyde and imine using standard procedures. The key cycloaddition step was performed by addition of a solution of LDA in THF to a cooled solution of imine **3** in THF. Addition of 1.7 equiv. of LDA (0.33 M solution in THF) to a cooled (-20 °C)

solution of **3a** and subsequent work-up afforded variable yields of a compound identified as **5a** from its being physically, analytically and spectroscopically identical to the product previously obtained using the imidate instead of the imine.[2] Assuming that **5a** was formed by generation of an aryne similar to **2**, intramolecular cycloaddition of the aryne and azadiene components to afford the intermediate **4a**, and oxidation of the latter to **5a** during the work-up, we oxidized the crude reaction mixture with $KMnO_4$; this afforded better, reproducible yields of **5a** (ca 50%). The use of 2.4 equivalents of LDA instead of 1.7 led to a mixture of **5a** (45%) and **5c** (R=OH, 9%), the latter probably having been formed by the nucleophilic attack of LDA on the methyl group of R in **3a**, **4a** or **5a**.



Scheme 1

Interestingly, treatment of imine **3b** with LDA (1.9 equivs., 0.24 M, -45°C) and subsequent oxidation with $KMnO_4$ afforded a mixture of amides **5b** (31%) and **7** (16%). Amide **5b** could be formed as above, while **7** would be the result of the regioisomeric cyclization to **6** in the key step. Both these products had also been obtained by cyclization of the corresponding imidates, but with inverse regioselectivity.[5]

Although further studies are necessary to evaluate the synthetic potential of this approach, it seems to complement that previously reported.

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