Study toward the total synthesis of lysicamine: an aporphine alkaloid with antileishmanial activity

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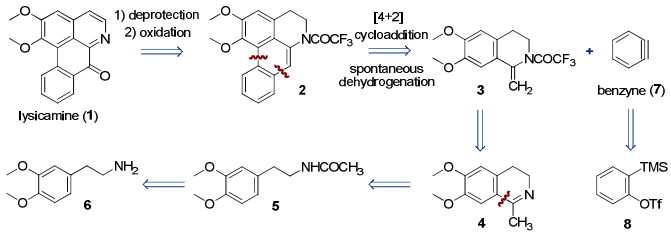
INTRODUCTION

Benzyne can be considered a highly reactive intermediate with application in reactions of insertion into sigma bonds and also in cycloaddition reactions, which have been broadly employed in total syntheses of bioactive natural products[1] and in preparations of functional materials.[2] Accordingly, we intend to accomplish the total synthesis of aporphine alkaloid named lysicamine (**1**),[3] a compound with antileishmanial activity,[4] employing strategy which has as key step the [4+2] cycloaddition reaction between 1-methylene-1,2,3,4-tetrahydroisoquinoline (**3**) and benzyne (**7**), generated from 2-(trimethylsilyl)phenyl triflate (**8**), under mild reaction conditions.

RESULTS AND DISCUSSION

Our approach to obtain lysicamine (**1**) was based on the retrosynthetic analysis outlined in **Scheme 1**.

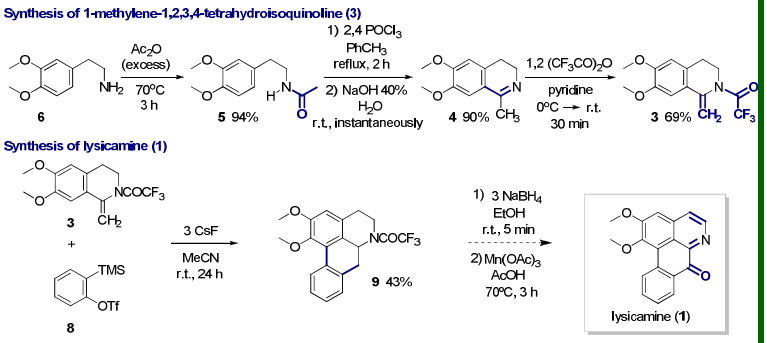
Scheme 1. Retrosynthetic analysis for lysicamine (**1**).



We started the synthesis of the aporphine alkaloid **1**, by the acetylation reaction of 3,4-dimethoxy-phenethylamine (**6**), with excess of acetic anhydride, resulting in the formation of 3,4-dimethoxy-phenethylamide (**5**) in 94% yield. Next, the reaction of the amide **5** with phosphorus oxychloride and subsequent acid-base reaction, led to the formation of 1-methyl-3,4-dihydroisoquinoline (**4**) in an isolated yield of 90%. The protection of the compound **4** with trifluoroacetic anhydride in pyridine gave the diene **3** (1-methylene-1,2,3,4-tetrahydroisoquinoline) in 70% yield. Afterwards, we carried out the [4+2] cycloaddition reaction between the compound **3** and the benzyne precursor **8**, in order to obtain the compound **9** in 43% yield (**Scheme 2**).

For our surprise the process of spontaneous dehydrogenation did not occur (**Schemes 1** and **2**).[3] The optimization of yield for the formation of the compound **9** is going to be carried out and the synthesis of lysicamine (**1**) will be completed from the intermediate **9** by well-known reactions of reduction[3] and oxidation[5] shown in **Scheme 2**.

Scheme 2. Synthetic rote for lysicamine (**1**).



CONCLUSION

The diene **3** was obtained by reactions that presented good yields. The [4+2] cycloaddition reaction between the compounds **3** and **8** led to the formation of the intermediate **9**. After optimization of the pericyclic reaction, lysicamine (**1**) will be produced by well-known transformations.

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