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

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INTRODUCTION

Benzene 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 and in preparations of functional materials. Accordingly, we intend to accomplish the total synthesis of aporphine alkaloid named lysicamine (1), a compound with antileishmanial activity, employing a 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-dimethoxyphenethylamine (6), with excess of acetic anhydride, resulting in the formation of 3,4-dimethoxyphenethylamide (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 benzene 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). 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 and oxidation shown in Scheme 2.

Scheme 2. Synthetic route 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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REFERENCES