Synthesis of analogs of Clauraila A

Fernando Fumagalli*; and Flavio da Silva Emery

School of Pharmaceutical Sciences of Ribeirão Preto (FCFRP-USP), Ribeirão Preto, São Paulo, Brazil
**nandofumagalli@hotmail.com*

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INTRODUCTION

The development of new bioactive compounds is necessary to address diseases that have few or no treatments. Diversity-oriented synthesis (DOS) helps in identifying hits and lead compounds, based on the prototypes with known biological activity. Natural products are good sources of bioactive compounds that can be used to design new drugs. The recently described carbazole alkaloid Clauraila A (Fig. 1)[1], isolated from *Clausena harmandiana*, is a typical example of the prototype compound that allows researchers to study structure-activity relationships for exploring the well-established cytotoxicity against human cell lung cancer.

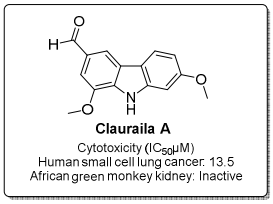
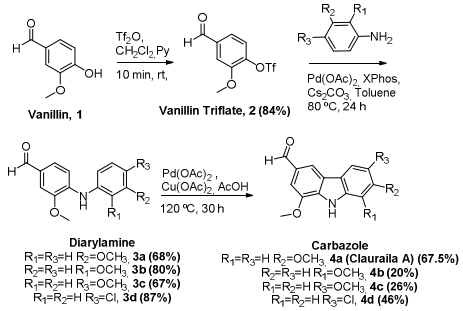


Figure 1 Structure and activity of Clauraila A[1]

The DOS strategy can be used to develop a carbazole library of Clauralia A analogs and thus diversify the building blocks for synthesizing heterocyclic derivatives.[2] Herein, we have optimized the synthesis of Clauraila A and analogs, with the aim of creating a carbazole library.

RESULTS AND DISCUSSION

Scheme 1 Outlines for the synthesis of carbazoles.



Scheme 1 Synthetic strategy for carbazoles

The Buchwald-Hartwig amination of the starting material, vanillin triflate, and different anilines afforded several diarylamines in 67-87% yields (Scheme 1). Next, palladium-mediated heterocyclization of diarylamines afforded the corresponding carbazoles in 20-67.5% yields (Scheme 1). Because the ideal reaction conditions of the Buchwald-Hartwig amination are specific for each pair of aniline and aryl triflate[3], we optimized the reaction conditions for the diarylamine synthesis, as shown in Table 1.

Table 1 Optimization of Buchwald-Hartwig amination reaction conditions for the synthesis of Clauraila A

Entry	Solvent	Base	Yield[a](%)[b]
1	Toluene	Cs_2CO_3	68 [30]
2	Toluene/*t*-butanol (5%)	Cs_2CO_3	50 [29]
3	Dioxane	Cs_2CO_3	38 [55]
4	Toluene	K_2CO_3	66 [28]

[a]Yield of isolated diarylamine; [b]percentage of vanillin triflate recovered

The best reaction conditions for the Buchwald-Hartwig amination were determined (Table 1, entry 1) and applied for the synthesis of Clauraila A analogs. Table 1 shows that increasing the base solubility by using highly polar solvents[4] did not increase the yield. Further, in the heterocyclization step (scheme 1), the diarylamine with an electron-donating group at the *meta* position shows higher reactivity as compared with the *ortho*- or *para*-substituted diarylamines[5], probably because of the higher electron density required for the C-H activation site.

CONCLUSION

This study enabled us to synthesize the natural product Clauraila A and three other analogues in good yields demonstrating the usefulness of the proposed strategy to create a carbazole library. Further, the effect of ring substituents on the reactions was analyzed. In the future, other anilines will be tested for a better understanding of their chemical reactivity toward heterocyclization.

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