Organoselenium functionalized nitrogen heterocycles: a proposition for new antimalarials.

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Keywords: S_NAr, pyridines, quinolones

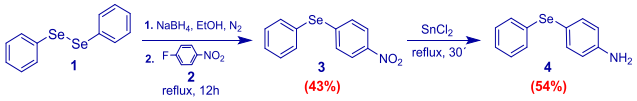
INTRODUCTION

Every year, approximately 250 millions of peoples are diagnosed with malaria.[1] The synthesis of hybrid compounds aims to maximize the performance of drugs.[2] Contemplating two distinct properties, the similarity with chloroquine and moiety containing selenium, as an inhibitor of proteases[3] involved in the life cycle of the parasite.

In this work, we realized synthesis of various hybrid compounds via nucleophilic aromatic substitution reactions between arilselenoaniline[4,5] and diclhoroquinolines and chloropyridines.

RESULTS AND DISCUSSION

The starting aniline **4** was synthetized from diphenyl diselenide (**1**) through a nucleophilic aromatic substitution using 4-nitrofluorbenzene (**2**) leading to the selenide **3** which was reduced using tin(II) chloride (Scheme 1).



Scheme 1. Synthesis of 4-(phenylseleno)aniline (**4**).

The aniline **4** was used as a model nucleophile to functionalize chloro-pyridines **5a-c**, 4,7-dichloroquinoline (**6a**) and 2,8-dicloroquinoline (**6b**) leading to amino-substituted nitrogen heterocycles (Chart 1).

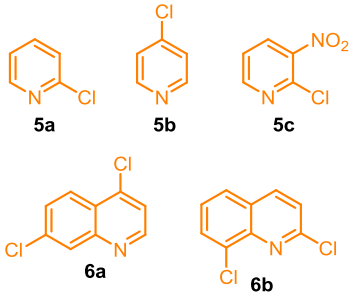
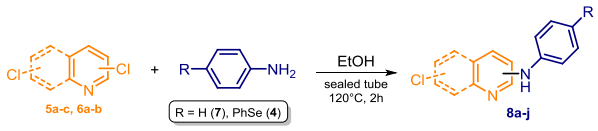


Chart 1. Structures of studied chloro-nitrogen heterocicles.

The functionalizations of heterocycles 5a-c and 6a-b were performed in a sealed tube using aniline (**7**) and the 4-(phenylseleno)aniline (**4**) in equimolar amounts of reagents in ethanol solution heated at 120°C for 2h as depicted in Scheme 2. Aniline (**7**) was used to compare the effect of the phenylselenenyl moiety in the relative reactivity and to parallel the biological studies using malaria enzymatic and cellular models.



Scheme 2. General reaction for the SNAr reactions.

The reactivity of pyridines and quinolones was distinct, the former were more reactive, especially pyridine **5c** and the latter less reactive. The difference on reactivity among **6a** and **6b** were remarkably distinct even with long reaction time (30h), the functionalization of **6b** showed to be more difficult. The reaction yields varied from poor to moderate yields.

CONCLUSION

This work show that nucleophilic aromatic substitution reactions were effective on obtainment of hybrid compounds of quinolines, pyridines and organoselenides for new drugs

ACKNOWLEDGEMENTS

UFABC for scholarship, CNPq and FAPESP for financial support. And Mirela I. Sairrê, Professor Ph.D. for RMN-H[1] characterization.

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