Synthesis of novel 4-amidopyranonaphthoquinone derived from nor-lapachol by Prins-Ritter reaction

Sandro J. Greco[1]*, Rodolfo G. Fiorot[1], Valdemar Lacerda Jr.[1], Reginaldo B. dos Santos[1], Illana M. C. B. da Silva[2], Vítor F. Ferreira[2] and Fernando de C. da Silva[2].

[1] *Laboratório de Pesquisas em Química Orgânica, DQUI, UFES, Av. Fernando Ferrari, 514, Vitória, ES;*
[2]*Universidade Federal Fluminense, Instituto de Química, GQO, Campus do Valonguinho, Niterói, RJ.*
**Corresponding author:* sandrogreco.ufes@gmail.com

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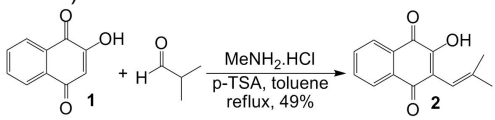
INTRODUCTION

The multi-component one-pot synthesis has received great importance because of its wide range of applications in pharmaceutical chemistry for the production of structural scaffolds and combinatorial libraries for drug discovery. In this context, three component coupling (3CC) reactions have proven remarkably successful in generating molecular complexities in a single step operation.[1] The 4-amidotetrahydropyran ring system is a core structure in a number of natural products[2] and generally, are prepared via Prins cyclization using acid catalysis. However, the use of Ritter amidation to terminate Prins cyclization is scarce, hence an efficient and practical methodology for the Prins-Ritter type reaction would be of great importance for the preparation of structurally diverse tetrahydropyran derivatives for the drug discovery process.

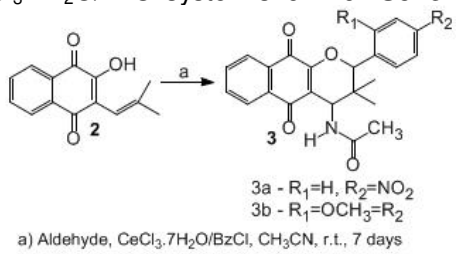
RESULTS AND DISCUSSION

Initially the nor-lapachol **2** was prepared through Mannich procedure followed by deamination (**Scheme 1**).[3]



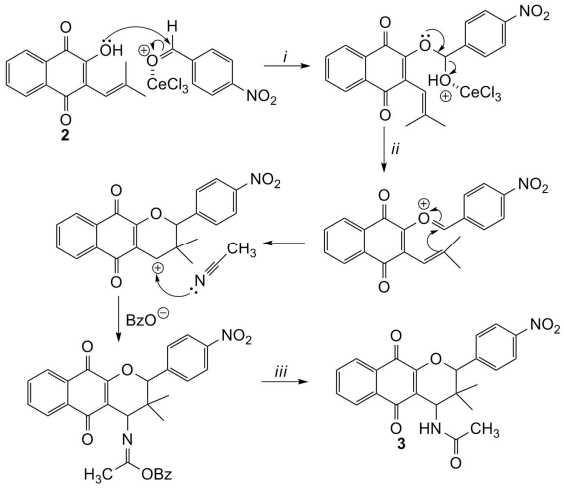
Scheme 1. Preparation of nor-lapachol.

The 4-amidopyranonaphthoquinones **3a** and **3b** were synthesized via a *Tandem* Prins-Ritter reaction with nor-lapachol **2** and p-nitrobenzaldehyde and 2,4-dimethoxybenzaldehyde, respectively, catalyzed by $CeCl_3.7H_2O$/BzCl system shown on **Scheme 2**.[4]



Scheme 2. Synthesis of 4-amidotetrahydropyran **3**.

No product was obtained when in absence of benzoyl chloride. On the other hand the reactions with BzCl proceeded satisfactorily leading to formation of products **3a** and **3b** with 55% and 50% of yield, respectively, after purification by column chromatography. The products were characterized by IR, ^1H and ^{13}C NMR. Currently, NOE experiments are being utilized to determine the stereochemistry of the molecules. The formation of the products could be explained by hemi-acetal formation (i) followed by Prins cyclization (ii) and subsequent Ritter amidation (iii) (**Scheme 3**).



Scheme 3. A plausible reaction mechanism.

CONCLUSION

In this work it was developed a methodology to prepare novel 4-amidopyranonaphthoquinone via Prins-Ritter reaction. Later it intends to investigate the scope and generality of this reaction using for this, various aldehydes and nitriles. All products should have obtained their antineoplastic activity tested in various cancer cell lines.

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