A New Method to Prepare 3-Alkyl-2-hydroxy-1,4-naphthoquinones. Synthesis of Lapachol and Phthiocol.

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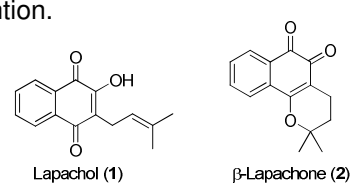
INTRODUCTION

Alkyl-1,4-naphthoquinones constitute an important group of compounds that present some types of biological activity. 3-Substituted-2-hydroxy-1,4-naphthoquinones such as lapachol (**1**) exhibit a broad spectrum of activities.[1] Lapachol (**1**)[2] is also widely used by the scientific community as a raw material for the synthesis of various bioactive derivatives and analogues, with β-lapachone (**2**) being one of the main lapachol derivatives.

For this reason, the isolation, structure elucidation and synthesis of 2-hydroxy-3-alkyl-1,4-naphthoquinones, especially lapachol, has attracted a lot of attention.

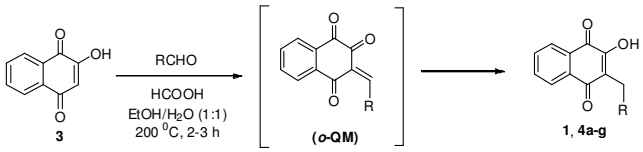


Lapachol (**1**) β-Lapachone (**2**)

Figure 1. Natural bioactive 3-substituted 1,4-naphthoquinones.

RESULTS AND DISCUSSION

In this methodology, lawsone (**3**) was used as the starting material, and it reacted with various aldehydes *via* the Knoevenagel condensation, followed by reduction of the *o*-QM formed *in situ* with formic acid at high temperature (Scheme 1). Using this protocol, it was possible to prepare in moderate to excellent yields several 3-alkyl derivatives of 2-hydroxy-1,4-naphthoquinone (**4a-g**), including lapachol (**1**), which are described in the Table 1.



3 (*o*-QM) 1, 4a-g

Scheme 1. Synthesis of 1,4-naphthoquinones **1** and **4a-g**.

The condensation and reduction reactions were performed in a closed steel reactor vessel in ethanol:water (1:1) using formic acid as reduction agent.This methodology is interesting because it could be employed to obtain 2-hydroxy-3-alkyl naphthoquinones in good yields without the possibility of formation *O*-alkylated by-products, one of the major problems encountered when alkylating 2-hydroxyquinones.

Table 1. Reduction of *o*-quinone methides to the corresponding 3-alkyl-2-hydroxy-1,4-naphthoquinones.

Product	R	Time (h)	Yield (%)
4a	-H	3	89
4b	-*p*-$NO_2C_6H_4$	2	90
4c	-C_6H_5	3	85
4d	-*p*-$OCH_3C_6H_4$	3	64
4e	-$CH(CH_3)_2$	3	78
4f	-$COCH_3$	3	45
4g	-$(CH_2)_3CHO$	3	60
1	-$CH=C(CH_3)_2$	3	78

CONCLUSION

In summary, this work describes the development of an alternative synthetic pathway for the reduction of the intermediate *o*-quinones methides *in situ* to perform selective C-alkylation of lawsone, producing the corresponding 1,4-naphthoquinone (**4a-g**) in moderate to good yields, especially the lapachol (**1**) in 78% yield. These results indicate that this reaction method is the most efficient method to date.

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