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

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Abstract: In this article a mild, simple, safe, and chemoselective synthesis and reduction of *o*-quinone methides to the corresponding 3-alkyl-2-hydroxy-1,4-naphthoquinones, compounds with interesting biological activity, mediated by the formic acid–water system is described. This new one-pot methodology was applied to the synthesis of lapachol and constitutes an efficient and inexpensive alternative for the preparation of this natural bioactive compound

Key words: reduction, quinones, alkylation, lapachol, phthiocol

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] Some 3-substituted-2- hydroxy-1,4-naphthoquinones **1**–**3** reported in the literature that highlight the importance of this class of compounds are presented in Figure 1.

The most prominent member of this group is lapachol (**1**)[2] which has inspired the synthesis of many compounds such as atovaquone (**3**). Lapachol (**1**) is a naturally occurring naphthoquinone found as a constituent of various plant families, including the *Bignoniaceae*, *Leguminosae*, *Sapotaceae*, *Scrophulariaceae*, *Verbenaceae*, *Malvaceae*, and *Proteaceae* and exhibits an impressive list of biological activities.[3] Its occurrence is prominent in the *Bignoniaceae* family, particularly in the genus *Tabebuia* (Tecoma). Lapachol was first isolated in 1882 from the *Tabebuia* species *avellanedae*.[4] These trees are commonly known in South America as Ipês, Lapacho, Pau d'Arco, purple and *lapacho Taheebo*.[5]

Since the discovery of the activity of **1** against Walker carcinoma 256,[6] several structural modifications have been introduced into the compound's structure to obtain new bioactive compounds against several pathogens.[7a–e]

Lapachol (**1**) has a prominent biological action and is widely used by the scientific community as a raw material for the synthesis of various bioactive derivatives and analogues, with β-lapachone (**4**) being one of the main lapachol derivatives. β-Lapachone (**4**) is currently being tested in a clinical phase II trial, under the code ARQ501, in combination with gemcitabine in a formulation with hydroxypropyl-β-cyclodextrin (HPβCD) for the treatment of pancreatic cancer.[8a,b]

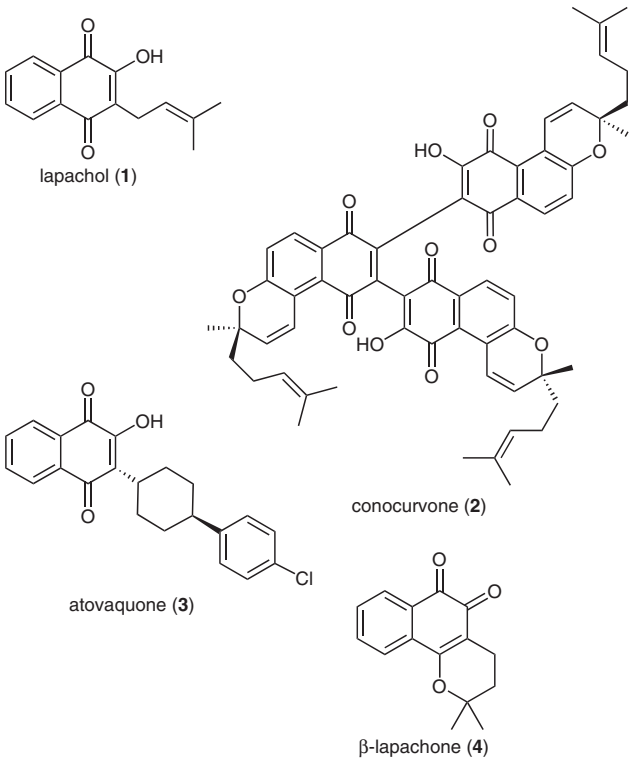

Figure 1 Natural and synthetic bioactive 3-substituted 1,4-naphthoquinones

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. This explains the fact that C–C bond-forming reactions providing lawsone (**5**) have become of great interest and have long been studied in the literature. In view of these facts, several methodologies have been described like coupling of

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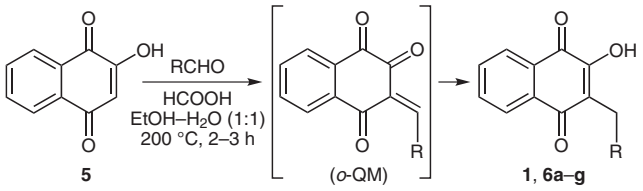
lawsone phenyliodonium ylide with activated arenes and aromatic aldehydes[9] and other coupling reactions[10,11] or different direct methods of alkylation, involving coupling of lawsone (**5**) with diazonium salts,[12] alkylation with trialkylboranes,[13] or addition of other alkylating agents to lawsone (**5**) and analogues.[14–16] One of the oldest methods was reported by Fieser;[17] this method performs the alkylation of the silver salt of lawsone (**5**) with 1-bromo-3-methyl-2-butene. Fieser also produced a panel of naphthoquinones possessing antimalarial activity by the reaction of diacyl peroxides with lawsone (**5**).[18]

The limitations of the above methodologies and our interest in the development of new synthetic approaches to prepare 2-hydroxy-1,4-naphthoquinones with important biological properties prompted us to explore the reduction of *o*-quinone methides (o-QM)[19a,b] generated in situ via the Knoevenagel condensation reaction between lawsone (**5**) and aldehydes (Scheme 1).



Scheme 1 Synthesis of 1,4-naphthoquinones **1** and **6a–g**

As in other methodologies, lawsone (**5**) was used as the starting material, and it reacted with various aldehydes, followed by reduction of the *o*-QM formed in situ with formic acid at high temperature. Using this protocol, it was possible to prepare in moderate to excellent yields several 3-alkyl derivatives of 2-hydroxy-1,4-naphthoquinone **6a–g**, including lapachol (**1**), which are described in Table 1.

The condensation and reduction reactions were performed in a closed steel reactor vessel in ethanol–water (1:1) using formic acid as reduction agent. Initially, the one-pot reaction was performed with formaldehyde, leading to the formation of **6a**, a commercial product known as phthiocol that is described as having molluscicidal activity.[20] It is worth noting that under these experimental conditions, if formaldehyde is used in excess, it can be oxidized by the oxygen in the air present inside the reactor vessel to formic acid,[21,22] which can then perform the reduction of the *o*-QM intermediate. The use of aldehydes as reagents and proreducing agents can only be applied for the preparation of **6a** or other naphthoquinones with a methyl group at position 3.

We next examined the formation and reduction of *o*-QM generated from other aldehydes, leading to substituted hydroxyl-naphthoquinones **1**, **6b–g**. The results indicated that we have developed a simple method for the reduction of *o*-quinone methides and an effective alternative to perform selective alkylation of lawsone (**5**). 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 byproducts, 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 under Optimized Reaction Conditions

Product	R	Time (h)	Yield (%)
6a[23]	H	3	89
6b[15]	4-$O_2NC_6H_4$	2	90
6c[9]	Ph	3	85
6d[24]	4-$MeOC_6H_4$	3	64
6e[25]	$CHMe_2$	3	78
6f[26]	COMe	3	45
6g	$(CH_2)_3CHO$	3	60
1[27]	$CH=CMe_2$	3	78

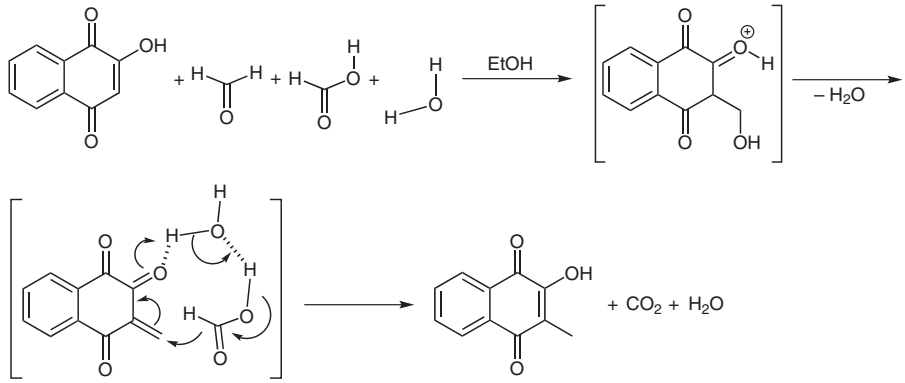
This protocol was used with different aldehydes to verify the versatility of the reaction; these aldehydes included those that contained aliphatic or benzyl substitutions with electron-withdrawing and electron-donor groups. The best yield was obtained for **6b**, which uses *p*-nitrobenzaldehyde, which contains a strong electron-withdrawing group, NO_2, that favors the condensation step. More interestingly, the use of a dialdehyde led selectively to the formation of **6g** in moderate yield without reduction of the terminal aldehydes.

The structures of compounds **1** and **6a–g** were confirmed by spectroscopic techniques, such as ^1H NMR and ^{13}C NMR and infrared (IR) spectroscopy, and these structures were identical to those reported in the literature.

To experimentally prove the need for water in the reduction of *o*-QM formed in situ, the reactions were performed in ethanol as the solvent (Scheme 2). The formation of the desired alkylated product was not observed in any of these reactions, and the starting material lawsone (**5**) was recovered.

As noted above, water participates actively in the course of this reaction, and this hypothesis is supported by previous reports in literature, which consider the participation of water on this reducing mechanism.[22]

To gain additional insight into the reaction mechanism, we carried out a set of DFT calculations for the reduction of the *o*-quinone methide by formic acid. After full optimization of a transition structure, we calculated an activation enthalpy of 17.8 kcal mol^{-1}. As the experimental results suggested a powerful effect of water on the reaction yield, we additionally optimized a transition structure in which one water molecule actively participates in the reduction process (see Figure 2 for both transition structures). The activation enthalpy in this case was reduced to 8.4 kcal mol^{-1}, therefore reinforcing the experimental evidence that the presence of water helps to reduce the acti-



Scheme 2 Proposed mechanism for the reduction of *o*-quinone methide by formic acid in water

vation energy. In summary, the DFT calculations provided further evidence for the reduction of quinone methides by formic acid, preferentially with one intervening water molecule.

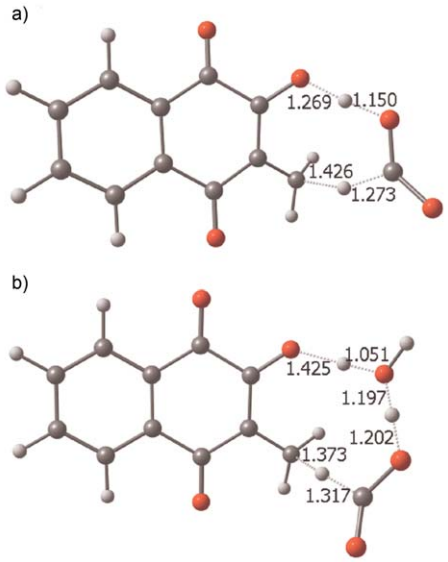


Figure 2 Optimized transition structures for reduction of *o*-QM by formic acid without (a) and with (b) the participation of one water molecule. Selected distances are given in Å.

In summary, this article 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 **6a–g** in moderate to good yields. This one-pot methodology was used in the synthesis of the natural product lapachol (**1**), which was obtained in 78% yield. Previous reports in literature showed the obtained compound **1** in 32% (after 3 steps)[27] and 43% (involving the use of palladium as catalyst and excess of reagents),[28] which indicates that our reaction method is the most efficient method to date.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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