Palladium-Catalyzed Allylation of 2-Hydroxy-1,4-naphthoquinone: Application to the Preparation of Lapachol

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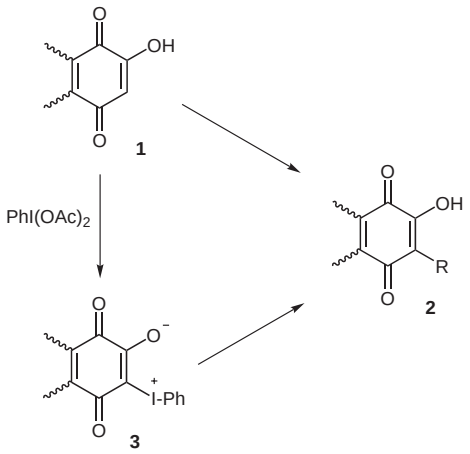
Abstract: The $Pd(PPh_3)_4$-catalyzed reaction of 2-hydroxy-1,4-naphthoquinone (lawsone) with allyl alcohols and allyl esters offers an easy access to 3-allyl-2-hydroxy-1,4-naphthoquinones, compounds with interesting biological activity. The reaction finds application in the preparation of lapachol. Other 2-hydroxy-1,4-benzoquinones give allylation products in low yields.

Keywords: allylation, lawsone, palladium-catalyzed, lapachol

Naturally occurring quinones constitute an important group of compounds, as the majority of them exhibit some kind of biological activity.[1] This activity becomes most intense and interesting in the case of a great variety of naturally occurring hydroxyquinones **1**, compounds with the hydroxyl in the quinone ring. For this reason isolation, structure elucidation and synthesis of hydroxyquinones has drawn a lot of attention[1] and their chemistry has been reviewed recently.[2]

Biologically active hydroxyquinones vary in structure complexity but in many cases 3-substituted hydroxyquinones **2** exhibit a broad spectrum of such activities. The carbon substituent R can be an alkyl, aryl, alkenyl or allyl group and most often has a simple structure. This explains the fact that C–C bond-forming reactions of hydroxyquinones leading to substituted derivatives **2** have become of interest. This functionalization can be achieved either directly or by the use of phenyliodonium ylides of hydroxyquinones **3**, the two routes presented in Scheme 1.

Ylides **3**, most easily prepared from the corresponding hydroxyquinones **1** and diacetoxyiodobenzene,[3] afford furonaphthoquinones in a Sonogashira-type coupling reaction with phenylacetylenes,[4] without isolation of the alkynyl intermediates, a reaction that can also proceed photochemically.[3a] Stagliano developed a Stille-type coupling methodology involving arylstannanes and aryliodonium ylides of hydroxyquinones,[3c,d] on his way to prepare trimeric quinones analogous to conocurvone, a natural product and potential anti-HIV agent. Recently, we reported[5] the copper-catalyzed coupling of phenyliodonium ylide of 2-hydroxy-1,4-naphthoquinone with indole derivatives to afford indolylquinones, a most interesting class of hydroxyquinones, related to the naturally occurring asterriquinones.[1,2] Finally, 2-aryl or 2-alkenyl-



Scheme 1 Routes to 3-substituted-2-hydroxy-1,4-quinones

hydroxyquinones are obtained from the Suzuki-type coupling of the corresponding ylides with aryl or alkenylboronic acids.[6]

Regarding the direct route (**1** → **2**), simple alkyl groups can be inserted by the use of either R_3B[7] or RTeTol,[8] and by radical coupling of hydroxyquinones with free alkyl radicals produced from the decarboxylation of the corresponding carboxylic acids.[9] Allyl groups can be inserted by a two-step sequence: formation of allyl ethers of 2-hydroxyquinones, under Mitsonubu reaction conditions, and Claisen rearrangement of the latter to the desired 3-allyl-2-hydroxy-1,4-quinones.[9,10]

Such allyl-substituted hydroxyquinones exhibit interesting biological activity, the most prominent members of the group being lapachol (**4**) and 2-(1,1-dimethyl-2-propenyl)-3-hydroxy-1,4-naphthoquinone (**5**), illustrated in Figure 1.

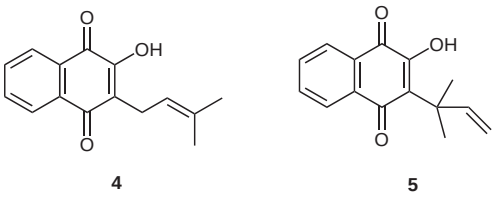


Figure 1 Structures of lapachol (**4**) and 2-(1,1-dimethyl-2-propenyl)-3-hydroxy-1,4-naphthoquinone (**5**)

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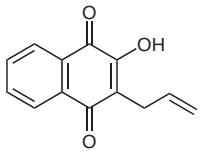
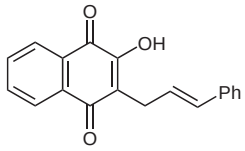
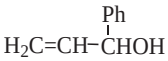
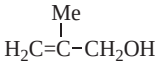
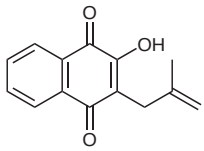
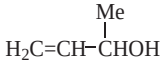
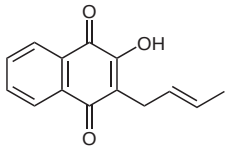
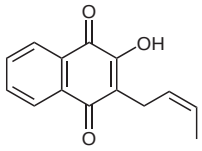
The importance of 3-allyl-2-hydroxyquinones prompted us to investigate the possibility of direct allylation of 2-hydroxyquinones, in order to access conveniently in one step this biologically active class of compounds. As reported recently, direct allylic substitution of various carbon nucleophiles can take place under Pd(0) catalysis either in a biphasic H_2O–EtOAc system[11] or in H_2O,[12] using allyl alcohols as allylating agents. In the second case acidic catalysis (with 1-adamantanecarboxylic acid) was necessary for the completion of the reaction. Later it was shown that allylic substitution of carbon nucleophiles can take place in the presence of a Pd(0)/carboxylic acid catalyst under neat conditions.[13]

In our case lawsone (**6**) was selected as the model hydroxyquinone, acting as a nucleophile, and the reaction was conducted using 0.9 mmol of **6**, 1.5 mmol of the allylating agent **7** (allyl alcohol or its acetate), $Pd(Ph_3P)_4$ (2 mol%) and two drops of AcOH, under neat conditions. After some experimentation with temperature and time it was found that best yields of the desired allyl compounds were obtained when the mixture was heated at 100 °C for 35 minutes[14] and the results with various allyl substrates are presented in Table 1.

The results of Table 1 show that the reaction affords similar yields of allylhydroxyquinones by using either allyl alcohols or their acetates as allylating agents (entries a, b and c, d). In the case of α-vinylbenzylalcohol (**7e**), the allylation product **8b** was identical to that obtained from the reaction with cinnamyl alcohol or its acetate (entries c and d). The same type of reactivity of α-vinylbenzyl and cinnamyl alcohol was reported in the Pd-catalyzed allylation of β-diketones in water.[12]

Analogous results are also obtained from the reaction of **6** with 3-buten-2-ol (**7g**) and crotyl alcohol (**7h**). In both cases an inseparable mixture of *trans* (as the main component) and *cis* isomers **8d** and **8e** was isolated. In

Table 1 Allylation of Lawsone (**6**) under Neat Conditions

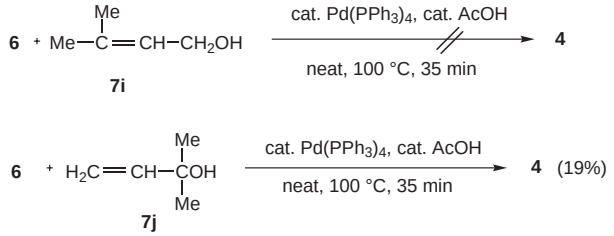
Entry	Allylating agent	Product			Yield (%)
a	H_2C=CH–CH_2OH **7a**	 **8a**			56
b	H_2C=CH–CH_2OCOMe **7b**	**8a**			60
c	PhCH=CH–CH_2OH **7c**	 **8b**			62
d	PhCH=CH–CH_2OCOMe **7d**	**8b**			52
e	 **7e**	**8b**			66
f	 **7f**	 **8c**			36
g	 **7g**	 **8d**	+	 **8e**	45 (**8d**:**8e**, 4:1)[a]
h	MeCH=CH–CH_2OH **7h**	**8d**	+	**8e**	38 (**8d**:**8e**, 5:1)[a]

[a] Estimated by ^{1}H NMR spectroscopy.

contrast, 2-methyl-2-propen-1-ol (**7f**) afforded the expected allylation product **8c**, albeit in lower yield.

Finally, no clear allylation product could be isolated from the reaction of **6** with geraniol, geraniol acetate and phytol as allylating agents.

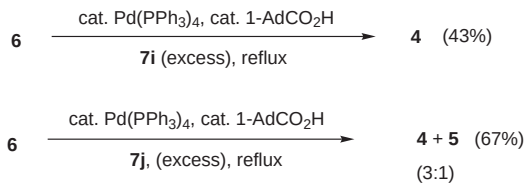
Based on the above results, the reaction of **6** with 3-methyl-2-buten-1-ol (**7i**) and 2-methyl-3-buten-2-ol (**7j**) would hopefully lead to the biologically active allylhydroxyquinones, lapachol (**4**) and 2-(1,1-dimethyl-2-propenyl)-3-hydroxy-1,4-naphthoquinone (**5**). In the first case the reaction with **7i**, conducted under the previously described conditions, failed to afford lapachol. In contrast, the corresponding reaction with **7j** afforded the desired lapachol **4** in 19% yield (Scheme 2).



Scheme 2 Reaction of lawsone with methyl butenols **7i** and **7j**

Aiming to the improvement of these results, the two reactions were repeated under slightly different conditions: a mixture of lawsone (0.9 mmol) and catalytic, as previously, amounts of $Pd(Ph_3P)_4$ and 1-adamantanecarboxylic acid was refluxed for 1 hour in an excess (4 mL) of the corresponding alcohol **7i** (bp 143–144 °C) or **7j** (bp 98–99 °C). After the usual work-up lapachol was isolated in 43% yield from the first reaction,[15] whereas the second reaction afforded a mixture of **4** and **5** (3:1, estimated by ^{1}H NMR spectroscopy) in 67% yield (Scheme 3).

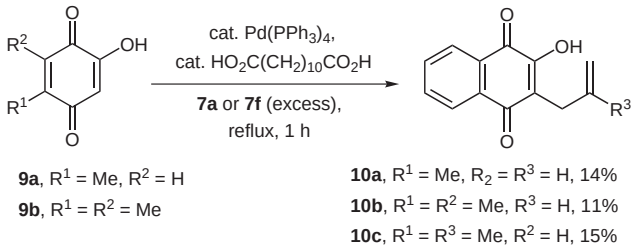
This mixture is inseparable by column chromatography but it can be separated by HPLC [column C18, mobile phase MeOH–MeCN–H_3PO_4 (0.1%), 25:45:10]. Moreover, an amount of pure lapachol, corresponding to 20–25% of the whole yield, can be obtained from this mixture by crystallization from hexanes.



Scheme 3 Modified conditions for the reaction of lawsone with methyl butenols **7i** and **7j**

The yields of lapachol (43% from the first reaction and 20–25% pure isolated from the second reaction) are considered satisfactory compared to the 40% yield of lapachol obtained according to a literature method.[16] This method, probably the most efficient one until now, involves the formation of the lithium salt of lawsone by addition of LiH to a frozen solution of the quinone in dimethyl sulfoxide and allylation with 3,3-dimethylallyl bromide. In this case a considerable amount (30%) of allylation takes place on the OH of lawsone, with the formation of the corresponding allyl ether as a by-product.

Finally, no allylation products were isolated from the reaction of other hydroxyquinones such as 5-methyl-2-hydroxy-1,4-benzoquinone (**9a**),[17a] 5,6-dimethyl-2-hydroxy-1,4-benzoquinone (**9b**)[17b] and 2-hydroxy-1,4-triptycenequinone[3e] under neat conditions. Such products were obtained only from the palladium-catalyzed reaction of quinones **9a** and **9b** (0.9 mmol) with excess (4 mL) of refluxing allyl alcohol (**7a**, bp 96–98 °C) or 2-methyl-2-propen-1-ol (**7f**, bp 113–115 °C), though in low yields (Scheme 4). In this case dodecanedioic acid was the proper acidic catalyst, as 1-adamantanecarboxylic acid was eluted from the chromatography column along with the allylation products **10**, making thus their separation and purification difficult. Under the same conditions 2-hydroxy-1,4-triptycenequinone failed again to afford allylation products.



Scheme 4 Allylation of benzoquinones **9**

In summary, transformation of lawsone to its 3-allyl derivatives can be achieved in one step by the Pd(0)- and acid-catalyzed reaction under neat conditions, using allyl alcohols or their acetates as allylating agents. The reaction can be used for the preparation of lapachol, an interesting biologically active compound and main precursor to the equally important naphthoquinone, β-lapachone.[16] Better yields of lapachol are obtained if the reaction is conducted in refluxing 3-methyl-2-buten-1-ol (**7i**). The same method affords allylation products of hydroxybenzoquinones with certain allylic alcohols but yields are considerably lower.

References and Notes

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(13) Patil, N. T.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 3101.
(14) **General Procedure for the Allylation Reaction of Lawsone under Neat Conditions.**
A mixture of lawsone (157 mg, 0.9 mmol), $Pd(Ph_3P)_4$ (50 mg, 0.045 mmol), AcOH (6 mg, 0.09 mmol, ca. 2 drops) and the proper allylating agent (alcohol or ester, 1.5 mmol) was thoroughly mixed and was put in an oven preheated at 100 °C. After 35 min the gummy material was subjected to column chromatography (silica gel, hexane–EtOAc, 5:1) to afford the allyl derivatives **8a**–**e**.
Representative Data for Allylation Products.
2-Hydroxy-3-(3-phenylallyl)-1,4-naphthoquinone (**8b**): mp 168–170 °C (lit.[18] 170 °C). IR (KBr): ν = 3289, 1671, 1641 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.14 (1 H, d, *J* = 7.3 Hz), 8.09 (1 H, d, *J* = 7.3 Hz), 7.77 (1 H, t, *J* = 7.3 Hz), 7.69 (1 H, t, *J* = 7.3 Hz), 7.41 (1 H, s, OH), 7.35–7.17 (5 H, m), 6.57 (1 H, d, *J* = 15.9 Hz), 6.30 (1 H, dt, J_1 = 15.9 Hz, J_2 = 7.5 Hz), 3.52 (2 H, d, *J* = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.3, 181.5, 153.1, 137.3, 135.0, 133.0, 132.0, 129.4, 128.4, 127.2, 126.9, 126.1, 125.4, 26.7. MS (EI): *m/z* (%) = 290 (94) [M^+], 199 (81), 91 (100). Anal. Calcd for $C_{19}H_{14}O_3$: C, 78.61; H, 4.86. Found: C, 78.42; H, 4.89.
(15) **Preparation of Lapachol (4).**
A mixture of lawsone (**6**, 157 mg, 0.9 mmol), $Pd(Ph_3P)_4$ (50 mg, 0.045 mmol), 1-AdCOOH (16 mg, 0.09 mmol) and 3-methyl-2-buten-1-ol (**7i**, 4 mL) was refluxed for 1 h. After removal of excess butenol in vacuum, the residue was subjected to column chromatography (silica gel, hexane–EtOAc, 5:1) to afford lapachol(**4**) in 43% yield; mp 137–139 °C (lit.[16] 139–140 °C) and ^1H NMR data identical to those reported in the literature.[16]
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