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# Regioselective Alkylation of Substituted Quinones by Trialkylboranes

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**Abstract:** 2-Methoxy-1,4-benzoquinone can be alkylated selectively with trialkylboranes in position 5, giving high yields of 5-alkyl-2-methoxy-1,4-benzoquinones after oxidative work up. In the case of 2-hydroxy-1,4-naphthoquinone, the same procedure leads to 3-alkylated products. A radical chain mechanism is proposed to explain the observed selectivity. 

*Keywords:* 1,4-Addition; trialkylboranes; 1,4-quinones; radical mechanism.

The conjugate addition of trialkylboranes to α,β-unsaturated carbonyl compounds is a well established synthetic method [1] and represents an interesting alternative to the more widely used addition of cuprates. In the special case of 1,4-benzoquinone, the procedure is superior to all other organometallic additions [2] producing high yields of monosubstituted hydroquinones.[3] In contrast to the preparative usefulness in the case of the unsubstituted parent compound, only one application to a symmetrically substituted 1,4-benzoquinone could be found in the literature.[4]

Motivated by our continuous interest in naturally occurring bioactive quinones, we performed some exploratory reactions in this field. Our first substrate, toluquinone, reacted smoothly at room temperature in THF with tri-n-butylborane. The crude reaction mixture was directly hydrolysed under oxidative conditions to the quinones because of their greater stability and easier spectroscopic identification, yielding a mixture of all three possible monoalkylated isomers. The chromatographic separation of the isomers, especially of the main products substituted in 5- and 6-position, proved to be extremely difficult reducing thus the preparative interest of the reaction. Similar disappointing results were obtained with 2-chloro-1,4-benzoquinone. However, when 2-methoxy-1,4-benzoquinone (**1**) [5] was used, 5-n-butyl-2-methoxy-1,4-benzoquinone (**2b**, R = n-Bu) was isolated in high yield as the only isomer.

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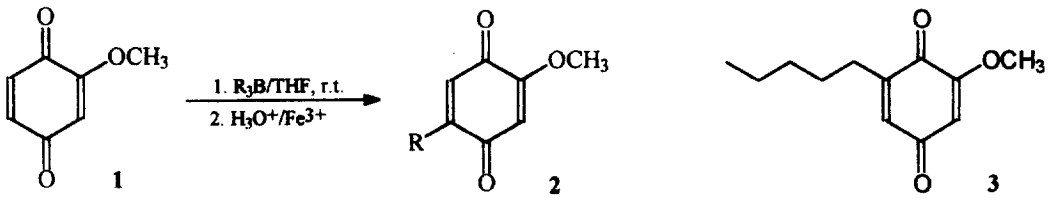



**Table 1.** Synthesis of alkyl-substituted 1,4-quinones by addition of trialkylboranes.[a]

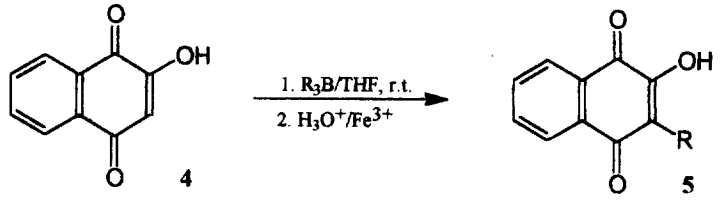
| Entry | Substrate | Product | R = | Yield(%) | m.p.(°C) |
|---|---|---|---|---|---|
| 1 | **1** | **2b** | n-butyl | 81 | 129-130 |
| 2 | **1** | **2c** | sec-butyl | 63 | 86-87 |
| 3 | **1** | **2d** | n-pentyl | 77 | 114-115 |
| 4 | **1** | **2e** | n-hexyl | 65 | 130-132 |
| 5 | **4** | **5a** | n-butyl | 85 | 93-94 |
| 6 | **4** | **5b** | sec-butyl | 68 | 82-83 |

a) Typical procedure: To a solution of the quinone (5 mmol) in 10 mL of dry THF was added a THF solution of the borane (6 mmol). After 2 h at r.t., the reaction was hydrolysed with 2N HCl / $FeCl_3$, the products were extracted with ether and purified by column chromatography.

The same regioselectivity was observed with sec-butylborane and with higher n-alkylboranes (table 1), opening a facile, one-step access to higher homologues of Coprinin (**2a,** R = Me), an antibiotic produced by the fungi *Coprinus radians* and *C. similis*.[6] Such compounds have been previously synthesized by a multistep procedure starting from resorcinol [7] and are of special interest as structural analogues of Primin (**3**), a potent anticancer agent,[8] but also one of the most active contact allergens found in nature.[9] Recent biological studies have shown that compounds of type **2** maintain the antitumour properties but have much lower allergenic activity and acute toxicity than their 6-substituted analogues.[10]

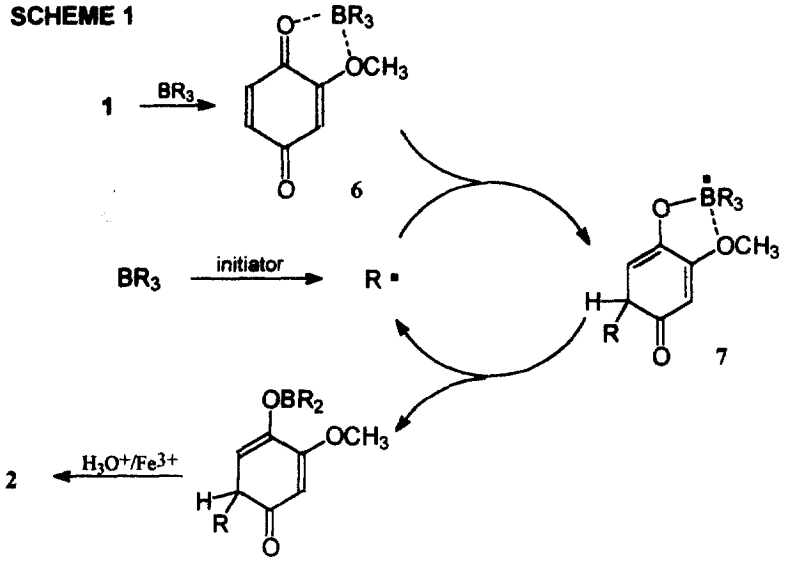
In order to obtain Coprinin (**2a**) itself, trimethylborane was generated from methyl magnesium iodide and $BF_3$ [11] and bubbled through a THF-solution of **1**, but the reaction proved to be completely unselective producing an unseparable mixture of all three isomers. Nevertheless, this synthetic limitation of the scope of the reaction seems rather acceptable, as the highly pyrophoric property of the reagent would discourage its use in preparative scale; furthermore, **2a** can be obtained from common methylsubstituted precursors by oxidative methods. [12]

On the other hand, the synthetic utility of the method could be demonstrated also in the case of 2-hydroxy 1,4-naphthoquinone (**4**, Lawsone) which was alkylated in high yield in position 3. Compounds of type **5** have been synthesized in the past as potential antimalarials via diacyl peroxide alkylation.[13] More recently, their antifungic and pesticidal properties have attracted new interest.[14]



A radical mechanism started by alkyl radicals is well documented for the borane addition to α,β-unsaturated carbonyl compounds [1] and unsubstituted 1,4-naphthoquinone.[15] However, the reaction of pentyl radicals generated by silver ion promoted decarboxylation of hexanoic acid in the presence of 1 has been reported to produce a mixture of all three possible isomers without any regioselectivity.[16] In our case, the observed selectivity may be explained by the formation of a quinone/borane complex **6** (scheme 1) which whould direct the attack of the radical to position 5 giving the intermediate **7**. This resonance stabilized radical can produce the borinate **8** liberating another alkyl radical to continue the chain. In the hydrolysis, **8** will be tautomerized, cleaved and oxidized to **2**. This mechanism explains the observed regioselectivity in the reaction of the higher trialkylboranes; non-coordinating substituents in the quinone or the extremely reactive trimethylborane will give a random attack in all possible positions.

**SCHEME 1**

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