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A NEW SYNTHESIS OF FUNCTIONALLY SUBSTITUTED HYDROQUINONES†

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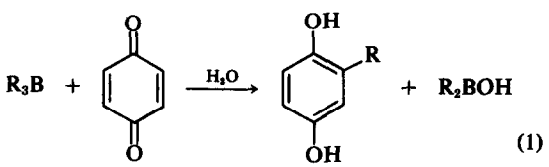
Abstract—Functionally substituted organoboranes readily react with *p*-benzoquinone yielding the corresponding functionally substituted hydroquinones in essentially quantitative yields.

INTRODUCTION

Alkylated hydroquinone and quinone substrates containing various functionalities in the alkyl group are of interest due to their deleterious effects on skin. The classical syntheses of alkylated hydroquinones and quinones (involving free radical alkylations,[1] Friedel Crafts acylation,[2] or modifications of naturally occurring quinones[3]) severely limit the types of functionalities that may be incorporated in the alkyl portion of the molecule.

Recently, the alkylation of quinone substrates in quantitative yields has been achieved via the reaction of organoboranes with various quinones.[4,5]



(1)

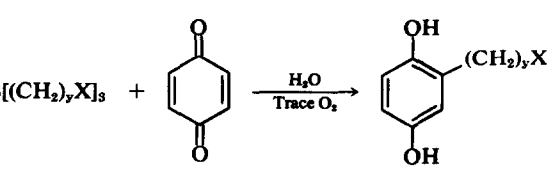
Organoboranes are unique among organometallic derivatives in that they can be synthesized containing a wide variety of functional groups.[6,7] We decided to ascertain whether the reactions of organoboranes with quinones could be expanded as a general synthesis of functionally substituted quinone systems through the utilization of functionally substituted organoboranes.

We have found this to be the case. Functionally substituted organoboranes readily react with *p*-benzoquinone to yield the corresponding hydroquinones in essentially quantitative yields, based on eq. 2.

RESULTS AND DISCUSSION

The preparation of functionally substituted organoboranes *via* the hydroboration of the corresponding functionally substituted olefins has been reported on numerous occasions.[6] A minor complication arises in these reactions that is dependent on the functionality present as well as its proximity to the reaction site. The complicating factor is that the regioselectivity of the hydroboration reaction is quite sensitive to electronic effects. In general, the normal regioselectivity of the hydroboration reaction is lessened as the functionality approaches the double bond (assuming a —I effect). For example, the hydroboration of propylene proceeds to place 94% of the boron at the terminal position. However, in the hydroboration of allyl benzoate, the percentage of the isomer containing boron at the terminal position drops to 70%.[6f] The directive effect of the various functionalities is decreased as their distance from the reaction site is increased. Thus the esters of 3-butenoic acid yield approximately 82% of the isomer containing boron at the terminal position whereas the esters of 4-pentenoic acid yield 93% of the isomer containing boron at the terminal position.[6e] For the esters of 10-undecenoic acid (in which the ester group is far from the reaction site) the normal distribution is generally observed.

Furthermore it has been demonstrated that, in the 1,4-addition reactions of organoboranes to α,β-unsaturated carbonyl compounds, secondary



(2)

where: y = 3, 4 or 10

x = Cl, —CO_2CH_3, —OCØ, —OCH_3

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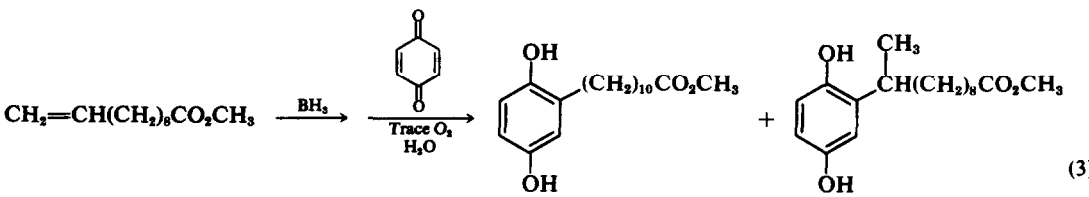
alkyl groups react preferentially to primary alkyl groups.[8] For example, the reaction of *tri*-butylborane (from the hydroboration of 1-butene) contains 6% of 2-butyl groups. Yet the products of the reaction of this borane with acrolein contains 15% of 4-methylhexanal.[8b] Thus most of the secondary alkyl groups present in the borane have reacted.*

Consequently it is not surprising to note that mixtures of isomers were normally obtained in our synthesis of functionally substituted hydroquinones. The exact ratio of isomeric products was dependent on the relative distribution of the boron in the organoborane. As an example, the hydroboration of methyl 10-undecenoate yields the trialkylborane containing 9% of the boron attached to the secondary position. Our results indicate that approximately 22% of the product was formed by attachment of the alkyl group at the secondary position.†

Quinone alkylations. The reactions were carried out as described previously.[5] In general, the trialkylborane was contained in a dry, N_2 flushed, 100 ml flask fitted with a septum inlet, magnetic stirrer, and a reflux condenser. Then water was added (necessary to hydrolyze the intermediate enol borinate) followed by *p*-benzoquinone in THF. Air was then passed into the flask at the rate of 0·1 ml/min through a syringe needle placed through the rubber septum cap. The reaction was followed by NMR spectroscopy. The progress of the reaction could be conveniently followed by monitoring the peak areas in the aromatic proton region of the spectra (*p*-xylene was utilized as an internal standard.) The reactions were normally complete within 30 min.

The yields were determined by NMR spectroscopy. Yields could be readily calculated after oxidation of aliquots of the reaction mixture with 2,3-dichloro-4,5-dicyanobenzoquinone (DDQ) or vanadium pentoxide-sodium chlorate.[9] The proton adjacent to the alkyl group in the alkylated quinones is shielded with respect to the other protons and appears at higher field generally at 6·6 δ).



(3)

The results are summarized in Table 1. The products in this study were isolated and characterized as the corresponding dimethyl ethers in an effort to minimize oxidative degradation during workup. The derivatives are summarized in Table 2.

EXPERIMENTAL

Hydroboration reactions. The hydroborations were carried out according to published procedures.[6] In general these involved the addition of 50 mmoles of borane (2·0 M in THF) to 150 mmoles of the neat olefin at 0°. As usual, all the hydroborations were carried out in nitrogen flushed, dry flasks fitted with septum inlets.[5] The hydroboration reactions were followed by NMR by observing the decrease in the area of the peaks due to the vinylic protons. In the case of allyl benzoate, a 30% excess of borane was added to compensate for the elimination-rehydroboration sequence.[6f]

Isolation. The products were converted to the corresponding dimethyl ethers to avoid oxidative degradation during characterization.

Synthesis of 5-methoxy-1-(2,5-dimethoxyphenyl)pentane. The general procedure has been previously described in detail.[5] Borane (50 mmoles, 25 ml of a 2 M soln in THF) was added to 150 mmoles (15·0 g) of 5-methoxy-1-pentene at 0°. After the hydroboration was complete, 50 mmoles (0·91 ml) water was added to the mixture followed by 50 mmoles (5·4 g) *p*-benzoquinone in 20 ml THF. The temp was kept at 0°. Air was added at the rate of 0·1 ml/min until the reaction was complete (~ 30 min). NMR analysis at this point indicated a 95% yield of the isomeric products.

Dimethyl sulfate (100 mmoles, 12·6 g) was added to the mixture followed by the addition of 100 mmoles of NaOH aq (33·3 ml of a 3 N soln). The mixture was warmed to 70° and maintained at that temp for 3 hr. After cooling to room temp, 50 ml ether was added to the mixture. The ether layer was separated from the aqueous layer washed once with water, dried over $MgSO_4$, and the ether removed under reduced pressure.

The crude product mixture was then separated by preparative gas chromatography (Varian Aerograph Model 711, 20 ft SE 30 on chromosorb W). The b.p. of a purified sample was measured as 175° at 1·55 mm; NMR (in CCl_4): δ = 6·4–6·6 (broad s, 3-H, ArH); δ = 3·6 (s, 6-H, Ar—O—CH_3); δ = 3·1 (broad s, 5-H, —CH_2—O—CH_3); δ = 2·25–2·65 (t, 2-H, Ar—CH_2—); δ = 1·2–1·7 (m, 6-H, —$CH_2CH_2CH_2$—).

Synthesis of 5-chloro-1-(2,5-dimethoxyphenyl)pentane. The procedure was essentially the same as that used for

*Since the 1,4-addition reaction of trialkylboranes utilizes one of the three alkyl groups on the boron atom, complete utilization of the secondary alkyl groups would lead to a maximum of 18% of the minor product.

†The isomeric quinone mixtures encountered in this study are quite readily separated via preparative gas chromotography. However, if desired, the relative amounts of the secondary isomers can be drastically reduced through the use of bisborinane or bis(3,5-dimethyl)borinane as the hydroborating agents. It has been demonstrated that the reaction of B-hexyl-(3,5-dimethyl)-borinane with methyl vinyl ketone yields 97% of 2-nonanone whereas trihexylborane yields only 85% of the primary isomer (nonanone) under identical conditions.[8]

Table 1. Conversion of functionally substituted olefins into the corresponding functionally substituted alkylated hydroquinones by the reaction of the corresponding organoborane with *p*-benzoquinone

Olefin	Products[a,b]	Yield, %[c]
Methyl 10-undecenoate	Methyl 11-(2,5-dihydroxyphenyl)undecanoate, 78 Methyl 10-(2,5-dihydroxyphenyl)undecanoate, 22	95
Methyl 3-butenoate	Methyl 4-(2,5-dihydroxyphenyl)butanoate, 64 Methyl 3-(2,5-dihydroxyphenyl)butanoate, 36	96
Allyl benzoate	3-(2,5-Dihydroxyphenyl)propyl benzoate, 70 2-*n*-Propyl-1,4-hydroquinone,[d] 30	94
3-Butenonitrile	4-(2,5-Dihydroxyphenyl)butyronitrile, 61 3-(2,5-Dihydroxyphenyl)butyronitrile, 39	90
5-Chloro-1-pentene	5-Chloro-1-(2,5-dihydroxyphenyl)pentane, 85 5-Chloro-2-(2,5-dihydroxyphenyl)pentane, 15	90
5-Methoxy-1-pentene	5-Methoxy-1-(2,5-dihydroxyphenyl)pentane, 82 5-Methoxy-2-(2,5-dihydroxyphenyl)pentane, 18	95

[a]The major products were isolated and characterized as their dimethyl ether derivatives. See Table 2. Structure assignments for minor products are based on NMR analysis.

[b]Isomer distributions were determined by GLC and NMR analysis of the dimethoxy derivatives.

[c]Yields were determined by NMR analysis of the hydroquinone as well as NMR analysis of the benzoquinone obtained by oxidation of aliquots of the reaction. Based on *p*-benzoquinone.

[d]The initial side product in this case readily eliminates the elements of boron and benzoate yielding 1-propene which is then hydroborated to yield the *n*-propyl derivative. See ref 6*f*.

Table 2. Summary of the derivatives utilized in product characterization

Product	Derivative	B.P. of derivative	Analyses found[a] (calc.) (%) C	H
Methyl 11-(2,5-dihydroxyphenyl)-undecanoate	11-(2,5-Dihydroxyphenyl)-undecanoic acid	m.p. 110–111°	69·36 (69·44)	8·90 (9·01)
Methyl 4-(2,5-dihydroxyphenyl)-butanoate	Methyl 4-(2,5-dimethoxyphenyl)-butanoate	188° at 3·5 mm	65·53 (65·67)	7·61 (7·63)
3-(2,5-Dihydroxyphenyl)propyl benzoate	3-(2,5-Dimethoxyphenyl)propanol	180° at 1·0 mm	67·32 (67·20)	8·22 (8·19)
5-Chloro-1-(2,5-dihydroxyphenyl)-pentane	5-Chloro-1-(2,5-dimethoxyphenyl)-pentane	190° at 1·55 mm	64·32 (64·12)	7·89 (8·00)
5-Methoxy-1-(2,5-dihydroxyphenyl)-pentane	5-Methoxy-1-(2,5-dimethoxyphenyl)-pentane	175° at 1·55 mm	70·56 (70·64)	9·30 (9·40)
4-(2,5-Dihydroxyphenyl)butyro-nitrile	Methyl 4-(2,5-dimethoxyphenyl)-butanoate	188° at 3·5 mm	65·53 (65·67)	7·61 (7·63)

[a]Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

the 5-methoxy-1-(2,5-dimethoxyphenyl)pentane. Borane (50 mmoles) was added to 150 mmoles (15·98 g) 5-chloro-1-pentene at 0°. After completion of the hydroboration, 50 mmoles water was added followed by 50 mmoles *p*-benzoquinone. Air was added at a rate of 0·1 ml/min until the reaction was complete. NMR analysis at this point indicated a 90% yield of the isomeric products.

Dimethyl sulfate (100 mmoles) was added to the mixture followed by 100 mmoles NaOH and the mixture maintained at 70° for 3 hr. After cooling, ether was added; the ether layer was then separated, washed once with water, dried over $MgSO_4$, and the ether removed under reduced pressure. The crude product mixture was separated by preparative GC (20 ft SE 30 on chromosorb W). The b.p. of the purified sample was measured as 190° at 1·55 mm; NMR (in CCl_4): $\delta = 6{\cdot}60$ (broad s, 3-H, Ar—H); $\delta = 3{\cdot}60$ (s, 6-H, $ArOCH_3$); $\delta = 3{\cdot}40$ (t, 2-H, $—CH_2Cl$); $\delta = 2{\cdot}48$ (t, 2-H, $ArCH_2—$); $\delta = 1{\cdot}10$–$1{\cdot}70$ (m, 6-H, $—CH_2CH_2CH_2—$).

Synthesis of methyl 4-(2,5-dihydroxyphenyl)butanoate

a. Utilizing methyl 3-butenoate. Borane (50 mmoles) was added to 150 mmoles (15·0 g) methyl 3-butenoate at 0°. After completion of the hydroboration, 50 mmoles water was added followed by 50 mmoles *p*-benzoquinone. Air was added at 0·1 ml/min until the reaction was complete. NMR analysis at this point indicated a 96% yield of the isomeric products.

Dimethyl sulfate (100 mmoles) was added to the mixture followed by the addition of 100 mmoles NaOH. The mixture was maintained at 70° for 3 hr. After cooling to room temp, the mixture was neutralized with HCl. Ether

was added, then the ether layer was separated, washed with water, dried over $MgSO_4$, and the ether removed under reduced pressure.

NMR analysis at this point indicated partial saponification. Anhydrous MeOH (25 ml) and one drop of methanesulfonic acid were added to the mixture and the mixture was stirred overnight at room temp. The MeOH was removed under reduced pressure and the isomeric product mixture was separated by preparative GC. The b.p. of the purified product was measured at 188° at 3·5 mm; NMR (in CCl_4): $\delta = 6{\cdot}60$ (broad s, 3-H, Ar—H); $\delta = 3{\cdot}60$ (s, 6-H, Ar—OCH_3); $\delta = 3{\cdot}45$ (s, 3-H, —CO_2CH_3); $\delta = 2{\cdot}10$–$2{\cdot}60$ (m, 2-H, $ArCH_2$—); $\delta = 2{\cdot}00$–$2{\cdot}30$ (m, 2-H, —CH_2CO_2R); $\delta = 1{\cdot}60$–$2{\cdot}00$ (m, 2-H, R—CH_2—R).

b. Utilizing 3-butenonitrile. Borane (50 mmoles) was added to 150 mmoles (10·1 g) 3-butenonitrile at 0°. After completion of the hydroboration, 50 mmoles water was added followed by 50 mmoles *p*-benzoquinone. Air was added at 0·1 ml/min until the reaction was complete. NMR analysis at this point indicated a 90% yield of the isomeric products.

Dimethyl sulfate (100 mmoles) was added to the mixture followed by the addition of 100 mmoles NaOH. The mixture was maintained at 70° for 3 hr. After cooling to room temp, ether was added. The ether layer was separated, washed once with water, and the ether removed under reduced pressure.

NMR and IR analysis of the mixture at this point indicated that the isomeric 3- and 4-(2,5-dimethoxyphenyl)-butyronitriles were the major products; NMR (in CCl_4): $\delta = 6{\cdot}60$–$6{\cdot}70$ (m, 3-H, Ar—H); $\delta = 3{\cdot}6$ (s, 6-H, $ArOCH_3$); $\delta = 2{\cdot}25$ (t, 2-H, —$CH_2C{\equiv}N$); $\delta = 2{\cdot}20$ (t, 2-H, $ArCH_2$—); $\delta = 1{\cdot}40$–$1{\cdot}60$ (m, 2-H, R—CH_2—R).

The mixture was added to a soln of 50 ml conc H_2SO_4 in 100 ml anhyd MeOH and the resultant mixture was refluxed overnight. The isomeric esters were isolated by carefully pouring the mixture into one liter of ice water and extracting the organic layer into ether. The ether layer was washed with Na_2CO_3 aq and water successively, then the ether layer was dried over $MgSO_4$ and the ether removed under reduced pressure. The product was isolated by preparative GC and its b.p. determined as 188° at 3·5 mm. NMR identical to that presented above in Part *a*.

Synthesis of 3-(2,5-dimethoxyphenyl)propanol. Borane (50 mmoles) was added to 150 mmoles (24·3 g) allyl benzoate at 0°. NMR analysis of the mixture, after 30 min, indicated that approximately 50 mmoles alkene remained in the mixture and no excess borane could be detected. This corresponds to a 33% loss of hydride which is in good agreement with the known behaviour of alkenes which contain good leaving groups adjacent to the double bond.[6f] (The benzoate group directs approximately 30% of the borane to the adjacent carbon yielding a 2-boro-1-propyl benzoate which readily eliminates the elements of boron and benzoate yielding propene which is then hydroborated.) The hydroboration was completed by the addition of 17 mmoles of borane.

Water (50 mmoles) was then added followed by 50 mmoles *p*-benzoquinone. Air was added at 0·1 ml/min until the reaction was complete. NMR analysis at this point indicated a 94% yield of alkylated hydroquinone.

Dimethyl sulfate (100 mmoles) was added, followed by 200 mmoles NaOH aq (sufficient excess to saponify the ester). The mixture was warmed to 70° and maintained at that temp for 5 hr. After cooling to room temp, ether was added to the mixture. The ether layer was separated from the aqueous layer, washed once with water, dried over $MgSO_4$, and the ether removed under reduced pressure. The crude product mixture was then separated by preparative GC. The b.p. of the purified product was measured at 180° at 1·0 mm; NMR (D_2O—CCl_4); $\delta = 6{\cdot}70$ (broad s, 3-H, Ar—H); $\delta = 3{\cdot}65$ (s, 6-H, $ArOCH_3$); $\delta = 3{\cdot}48$ (t, 2-H, R—CH_2—O—); $\delta = 2{\cdot}58$ (t, 2-H, Ar—CH_2—); $\delta = 1{\cdot}40$–$1{\cdot}85$ (m, 2-H, R—CH_2—R).

Synthesis of 11-(2,5-dihydroxyphenyl)undecanoic acid. Borane (50 mmoles) was added to 150 mmoles (29·7 g) methyl 10-undecenoate at 0°. After completion of the hydroboration, 50 mmoles water was added followed by 50 mmoles *p*-benzoquinone. Air was added at a rate of 0·1 ml/min until the reaction was complete. NMR analysis at this point indicated a 95% yield of the isomeric products.

The mixture was maintained under N_2 and 200 mmoles NaOH were added to the mixture (sufficient excess to saponify the ester). The mixture was stirred for 3 hr under N_2. The mixture was extracted with two 25 ml aliquots of ether to remove the organic, non-acidic side products. The alkaline water layer was then neutralized with HCl and the organic layer extracted into ether. The resultant oil was comprised chiefly of the isomeric undecanoic acids. (The presence of boron containing products was detected also, presumably borinic and boronic acids). The recovery of crude product was approximately 80%. The 11-(2,5-dihydroxyphenyl)undecanoic acid was purified by recrystallization from ether-hexane. The m.p. observed was 110–111°; NMR (D_2O—$CD_3\overset{O}{\overset{\|}{C}}CD_3$); $\delta = 6{\cdot}75$ (broad s, 3-H, Ar—H); $\delta = 2{\cdot}1$–$2{\cdot}4$ (m, 2-H, $ArCH_2$—); $\delta = 1{\cdot}20$–$1{\cdot}70$ (m, 18-H, $-CH_2C(=O)-O-$ and alkyl H).

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