Tetrahedron Letters 51 (2010) 3033–3036

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Reductive alkylation of *p*-benzoquinone using mixed organoboranes

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ARTICLE INFO

Article history:
Received 17 December 2009
Revised 19 March 2010
Accepted 23 March 2010
Available online 27 March 2010

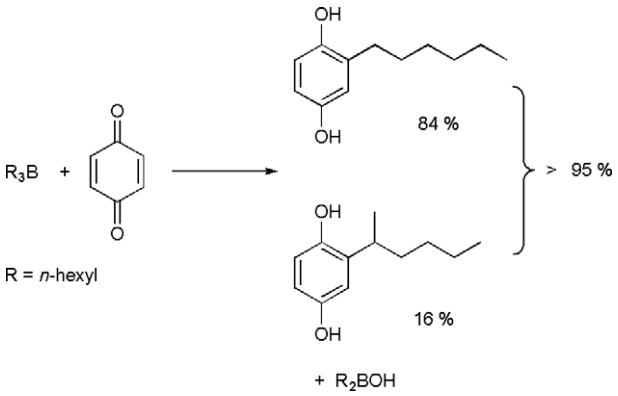
Keywords:
p-Benzoquinone
Hydroquinones
Reductive alkylation
Organoboranes
Alkyldimethylboranes

ABSTRACT

Mixed organoboranes based on diphenyl- or dimethylalkylboranes transfer the alkyl group in the reductive alkylation of *p*-benzoquinone to form the alkylhydroquinones in very high yields. The auxiliary groups do not transfer or have a low migratory aptitude. Primary and secondary alkyl groups are transferred with retention of regio- and stereochemistry to the hydroquinone. O-Alkylation is the major product with tertiary and secondary groups with steric bulk in proximity to the site of attachment. The presence of metal salts, such as magnesium, results in reduction to the unsubstituted hydroquinone. This reaction makes the first practical route to alkylhydroquinones via organoboranes.

Substituted hydroquinones and the related quinones are found extensively in nature and many have important biological activity.[1] Relatively few general methods exist for the formation of the crucial carbon–carbon bond between the ring and alkyl carbon. Most techniques depend on the oxidation of substituted phenols to *p*-benzoquinone, the majority of which form mixtures or at best result in moderate yields.[2] The Stille and Suzuki reactions give improved carbon–carbon bond formation; they are versatile and tolerant of a wide variety of functional groups, but are essentially restricted to aryl and vinyl groups for good to high yields.[3,4] Quinone or hydroquinone derivatives have been prepared to a limited extent by these metal-catalyzed reactions. The limitations of these reactions include the synthesis of the aryl- and vinyl-boranes, as well as the tin reagents. In addition, the toxicity of the latter, even at trace levels, along with the difficulty of removing the palladium catalysts, is a concern in biological and medicinal applications. Moreover, the palladium ligands and co-catalysts usually require reaction condition optimization in order to maximize yields. While promising, these two reactions are not applicable to secondary alkyl groups and give reduced yields for primary alkyl groups.

Hawthorne and Reintjes discovered one of the first organoborane reactions after the discovery of hydroboration, the reductive alkylation of quinone using symmetrical trialkylboranes.[5,6] The alkyl hydroquinone products were rapidly formed in essentially quantitative yield. Kabalka noted the similarities of this reaction to the 1,4-addition of organoboranes to α,β-unsaturated aldehydes and ketones, in which both reactions had radical character, transferring only one alkyl group.[7] As in the 1,4-addition, Kabalka found that the reductive alkylation of *p*-benzoquinone resulted in the formation of a mixture of isomeric alkyl hydroquinone products.[8] This was attributed to the higher migratory aptitude of the more substituted alkyl groups. While the regioselectivity in the hydroboration of 1-alkenes using BH_3·THF is approximately 94:6, primary to secondary, the majority of the secondary alkyl groups were preferentially transferred, giving approximately 16% of the isomeric hydroquinone product (Scheme 1). This regioselectivity decreases in proximity of the alkene to many of the functional groups due to directive effects. Although substituted hydroborating agents, such as 9-BBN, disiamyl, and dicyclohexylborane, give higher regioselectivities, these hydroborating reagents are based on second-



Scheme 1. Isomeric products formed with trihexylborane.

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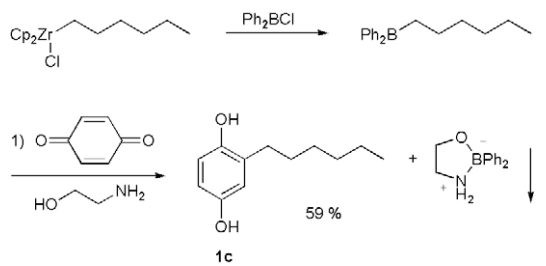
doi:10.1016/j.tetlet.2010.03.096

ary alkyl auxiliary groups. These auxiliary groups transfer competitively or faster than the desired group. Only one alkyl group of a trialkylborane is transferred in the reductive alkylation of *p*-benzoquinone. This results in the loss of two potentially valuable alkyl groups in reactions with symmetrical trialkylboranes. Separation of the formed borinic acids, especially those with larger alkyl groups, using either steam distillation or oxidation presents additional problems. The borinic acids generate radicals on exposure to air, which are trapped by the hydroquinone product, forming a tarry product. This complicates isolation and lowers the purity and yields of the alkylated hydroquinone products. It is for these reasons that this reaction has not found widespread application.

More recently, Renaud and co-workers demonstrated the reductive alkylation of *p*-benzoquinone using B-alkylcatecholboranes, forming the corresponding alkylhydroquinones in moderate to excellent yields.[9] The *N,N*-dimethylacetamide-catalyzed hydroborations using catecholborane gave lower regioselectivity than catecholborane, approximating that of BH_3.[10] This resulted in an isomeric mixture of alkylhydroquinone products. In addition, a 100 mol % excess of the alkylcatecholborane was used. Renaud found that increasing amounts of alkyl–aryl ether products were formed with increasing steric bulk about the boron–carbon bond. This O-alkylation was the dominant product with tertiary alkyl catecholboranes. Overall, Renaud's results represented a significant improvement for the reductive alkylation of *p*-benzoquinone. We have been exploring new routes to mixed organoboranes, which may permit the development of the reductive alkylation of *p*-benzoquinone using organoboranes into a more versatile and valuable reaction.

Hawthorne's observation that triphenylborane did not react with *p*-benzoquinone suggests that the phenyl group may be a suitable auxiliary group for these reductive alkylations using mixed organoboranes, Ph_2BR. Earlier attempts to prepare mixed arylalkylboranes generally gave little of the expected product, mainly forming the disproportionation products, symmetrical triphenyl- and trialkylboranes. Recently, we have developed a successful preparation of alkyldiphenylboranes using the transmetallation of alkyl groups from a zirconocene complex to diphenylchloroborane.[11] The alkylzirconocene chloride is formed by the hydrozirconation of the corresponding alkene using Schwartz's reagent. The alkyl group is formed with high regioselectivity, giving >99.6% in the terminal position for 1-alkenes. The addition of 1 equiv of 1-hexyldiphenylborane to a quinone solution showed a rapid disappearance of its yellow color. The diphenylborinic acid was precipitated by complexation with ethanolamine. The solvent was removed and the crude hexylhydroquinone product was recrystallized in a 59% yield (Scheme. 2). The proton NMR showed only mono-alkylation with no detectable presence of phenylhydroquinone. While other alkyldiphenylboranes can also be used for the reductive alkylation of *p*-benzoquinone, the types of alkyl groups that can be cleanly formed by hydrozirconation are limited.

The migratory aptitudes shown for this reaction, the related 1,4-addition to α,β-unsaturated aldehydes and ketones and their radical characteristics suggest that the methyl group may also serve as a suitable auxiliary group for these reactions. There are several routes that can be used to prepare alkyldimethylboranes.



Scheme 2. Reductive alkylation of quinone using hexyldiphenylborane.

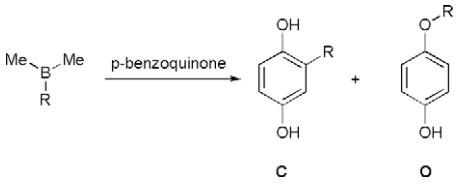
In this study, we chose dichloroborane as the hydroborating agent, since it is one of the most regioselective hydroborating agents, giving ⩾99% of the 1-alkyl group for terminal alkenes.[12] The chlorines can be replaced with methyl groups, yielding the alkyldimethylborane. Matteson's procedure for the in situ generation of dichloroborane gave excellent selectivities in forming the alkyldichloroborane, ⩾96%.[13] This method is superior to the coordinated dichloroborane reagents, $HBCl_2{\cdot}L$, which require an equivalent of boron trichloride to remove the ligand.[14] In addition, the presence of boron trichloride potentially complicates the methylation of the alkyldichloroborane.

Addition of a triethylsilane and 1-hexene mixture to boron trichloride cleanly yielded the 1-hexyldichloroborane. The boron NMR analysis of the methanolyzed reaction mixture showed a greater than 98% selectivity in the formation of the alkyldichloroborane, with approximately equal amounts of dihexylchloroborane and boron trichloride. The 1-hexyldichloroborane solution was then added to 2 equiv of methylmagnesium bromide in THF/Et_2O. The ratio of alkylmethylboranes can be readily determined from the ^{11}B NMR spectrum. Tetrahydrofuran complexes to the methylboranes, shifting their resonance signals upfield proportional to the number of methyl groups. These ratios of the methylboranes were essentially identical to the purity of the alkylchloroboranes, showing very little, if any, redistribution. By contrast, the addition of the methyl Grignard reagent in Et_2O to the hexyldichloroborane resulted in significant amount of redistribution, forming ca. 20 mol % each of trimethyl- and dihexylmethylborane.[15]

The addition of *p*-benzoquinone to the above-mentioned alkyldimethylborane solution, containing magnesium salts, resulted mainly in the reduction of the quinone, forming >80% of the non-alkylated hydroquinone. Washing of the alkyldimethylborane solution with water, 4 × 10 mL, before the addition of *p*-benzoquinone, reduced the amount of hydroquinone to less than 5%. The dropwise addition of a ca. 1 M THF solution of *p*-benzoquinone at room temperature showed a fast disappearance of its yellow color until about 95 mol % or more had been added. The boron NMR spectrum showed quantitative formation of the borinic acid as seen at 52 ppm. The volatile dimethylborinic acid and solvents were removed under vacuum to give an off-white crude product. The proton NMR showed ⩽4 mol % hydroquinone (6.72 ppm), trace amounts of methylhydroquinone (2.12 ppm) and 95 mol % hexylhydroquinone. The hydroquinone was removed in a water wash and the product **1c** was purified by column chromatography and recrystallized from hexane–ethyl acetate to give a 94% yield **1c**, Table 1. The reaction of trimethylborane and *p*-benzoquinone under essentially identical conditions was considerably slower, taking at least 2 h to react with the *p*-benzoquinone. Analysis of the products showed little of the expected methylhydroquinone product, ca. ⩽15%, and the formation of a complex mixture of unidentified products. Thus, indicating that the methyl group will be a valuable auxiliary.

Other primary alkyl groups, such as (4-cyclohexenylethyl)-**2c** and (2-phenylpropyl) **3c** give 88% and 84% yields of the corresponding alkylated hydroquinone products. Secondary alkyl groups, such as cyclohexyl, are cleanly transferred in the reductive alkylation forming cyclohexylhydroquinone **4c** in an isolated yield of 93%. While this reductive alkylation reaction has radical character, it is important to establish whether this affects the stereochemically defined alkyl groups. The hydroboration of norbornene with dichloroborane forms the *exo* isomer with a selectivity of 99.5%.[16] The reductive alkylation of quinone with (*exo*)-norbornyldimethylborane proceeds smoothly to give an isolated yield of 73% of the (*exo*)-norbornylhydroquinone **5c**. A proton NMR analysis of the crude

Table 1
Yields of 2-alkyl-hydroquinones via reductive alkylation using mixed organoboranes[a]



Entry	Alkyl group	%Yield[b] **c**	%Yield[b] **o**
1	1-Hexyl-	**1c**, 59,[c] 94	**1o**, Trace
2	2-Ethylcyclohex-3-enyl-	**2c**, 88	**2o**, Trace
3	2-Phenylpropyl-	**3c**, 84	**3o**, Trace
4	Cyclohexyl-	**4c**, 93	**4o**, Trace
5	(*exo*)-Norbornyl-	**5c**, 73	**5o**, Trace
6	2-Methylcyclohexyl-	**6c**, 65[d]	**6o**, 14[d]
	trans:*cis*	94:6	77:23
7	(+)-Isopinocampheyl-	**7c**, 42	**7o**, 41

[a] All reactions were carried out under an inert nitrogen atmosphere using the typical reaction procedure.[20]
[b] Yield of isolated products.
[c] Yield based on diphenyl-1-hexylborane.
[d] These products were isolated as a mixture and their ratios were determined by ^{1}H NMR spectroscopic data.

product mixture showed no signals at ca. 3.2 ppm, for the *endo* isomer. This result is similar to that observed in earlier 1,4-additions studies.[17] The X-ray structure, Figure 1, indicates the (*exo*)-norbornylhydroquinone product.[18] The hydroboration of 1-methylcyclohexene yields, with high stereoselectivity, the *trans*-2-methyl cyclohexylborane via the *syn* addition of dichloroborane. Methylation of the alkyldichloroborane followed by reaction with quinone gave two isomeric products in a 94:6 ratio with an overall yield of 65% for ***trans*-6c** and ***cis*-6c**. These ratios are consistent with those based on mechanics or semi-empirical calculations. The hydroboration of 88% ee (+) α-pinene[19] with dichloroborane, methylation, and the reductive alkylation of *p*-benzoquinone gave the 2-isopinocampheylhydroquinone **7c** in a 42% isolated yield as a single isomer in this sterically biased group. The optical purity was determined by converting the purified hydroquinone product to the 4-pivaloyl mono ester then reacting with the S-(+)-MTPA-Cl. The ratios of the diastereomeric NMR proton signals for the methoxy, hydroquinone, and phenyl groups gave an 88.2% de average while the ^{19}F NMR signals for the trifluoromethyl group gave an 89.9% de. All of these values are within experimental error indicating little, if any, loss of chirality on transfer of the isopinocampheyl group.

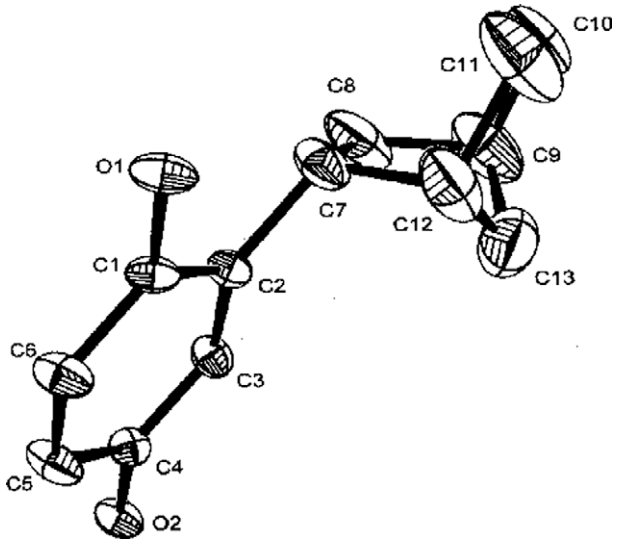


Figure 1. ORTEP drawing of **5c**.

The reaction of 1,1,2-trimethylpropyldimethylborane (dimethylthexylborane) gave little thexylhydroquinone, 22%, while O-alkylation was the dominant product, 78%, as reported by Renaud.[9] We did not further investigate the reductive alkylations of tertiary-alkyldimethylboranes since there are a limited number of tertiary alkylboranes that can be formed and the low yields of the alkylated hydroquinones. The amount of O-alkylation appears to be dependent on the steric bulk in proximity to the boron–carbon bond. All the primary and the secondary alkyl groups, cyclohexyl- and (*exo*)-norbornyl **1–5**, gave only trace amounts, <1%, of O-alkylated ether product. These aryl–alkyl ethers are observed slightly downfield, as a symmetric multiplet, from the hydroquinone product. Increasing steric bulk in the proximity of the boron attachment in the (*trans*)-2-methylcyclohexyl- and isopinocampheyl- groups gave increasing amounts of O-alkylation, 14% **6o** and 41% **7o**, respectively. The methylcyclohexyl group gave both *trans* and *cis* O-alkylation products in a 77:23 ratio. These ratios are in agreement with calculated energies for both the C- and O-alkylation products. On the other hand, the stereochemistry of the isopinocampheyl group was completely retained for both C- and O-alkylation.

In conclusion, high yields of primary and secondary alkyl hydroquinones are obtained in the reductive alkylation of *p*-benzoquinone using alkyldimethylboranes. There is little, if any, migration of the methyl auxiliary group. The corresponding borinic acids can readily be removed from the reaction mixture resulting in improved product purity and yields. O-alkylation becomes more significant with increasing bulk about the boron–carbon bond and can result in a loss of stereochemistry.

Acknowledgments

We thank the San Diego Foundation, Blasker Foundation for financial support of this project. We also acknowledge Professor Carl Carrano and Mr. Justin Hoffman for the characterization of the X-ray structure of the (*exo*)-norbornylhydroquinone. We also thank Drs. Ratnasamy Somanathan and LeRoy Lafferty for their valuable assistance in the NMR and stereochemical determination of the products. Finally, we dedicate this research to Dr. Clinton Lane whose contributions and encouragement will be missed by many.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.03.096.

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18. The crystal of **5c** has been deposited in CCDC with number 719666. Empirical formula: $C_{13}H_{16}O_2$; formula weight: 204.26; crystal size: 0.8 × 0.1 × 0.1 mm; crystal color, habit: colorless, prismatic; crystal system: tetragonal; parameters: a = 18.677(2) Å, b = 18.677(2) Å, c = 13.094(2) Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, V = 4567.4 Å^3; space group: *P4nc*; Z = 18; D_{calcd} = 1.188 g/cm^3; F_{000} = 1760; R_1 = 0.0828, wR_2 = 0.2334. Diffractometer: Bruker X8 Apex.
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20. *Typical reaction procedure* (Table 1, *entry 1*): A mixture of 5 mmol each of triethylsilane and 1-hexene was transferred by double ended needle over 15 min to 5 mmol of BCl_3 in hexane, stirred at 0 °C for 4 h, then allowed to warm to room temperature. The resulting hexyldichloroborane was quickly transferred by double ended needle to 10 mmol of MeMgBr in ethyl ether (3.33 mL) and THF (10 mL), cooled to 5 °C, and stirred for an additional 30 min, then warmed to room temperature. Magnesium salts were removed by washing with water (4 × 10 mL). A solution of 4.75 mmol *p*-benzoquinone dissolved in THF was added dropwise by syringe at room temperature and stirred for 30 min. Solvents and Me_2BOH were removed under vacuum. The crude reaction mixture was dissolved in methylene chloride, washed with water, saturated sodium chloride, and dried with magnesium sulfate. The organics were evaporated onto silica gel and eluted with hexanes followed by hexanes/ethyl acetate (80:20). The hexanes/ethyl acetate fraction was evaporated under vacuum and the residue recrystallized from hexanes/ethyl acetate to afford compound **1c** in a 94% yield as a white solid, mp 81.5–82.7 °C; IR (KBr pellet), 3400–3100 (br), 2955, 2929, 2856, 1618, 1518, 1376, 1196, 863, 815 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.63 (d, J = 8.5 Hz, 1H), 6.62 (d, J = 3.0 Hz, 1H), 6.54 (dd, J = 8.5, 3.0 Hz, 1H), 4.57 (s, 1H), 4.46 (s, 1H), 2.53 (t, J = 7.75 Hz, 2H), 1.58 (quintet, J = 7.6 Hz, 2H), 1.36 (m, 2H), 1.30 (m, 4H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.31, 147.39, 130.11, 116.85, 116.06, 113.30, 31.75, 30.05, 29.65, 29.18, 22.62, 14.09.