



Synthesis of 2-substituted hydroquinone derivatives from 1,4-benzoquinone and allyl ethers

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ARTICLE INFO

Article history:

Received 4 December 2017

Received in revised form

24 January 2018

Accepted 26 January 2018

Available online 22 March 2018

Keywords:

Hydroboration

Hydroquinone

Benzoquinone

Wilkinson's catalyst

ABSTRACT

B-Alkylpinacolboranes, derived from rhodium-catalyzed hydroboration of allyl ethers with pinacolborane, react with 1,4-benzoquinone under acidic, oxidizing conditions, to afford, after subsequent hydrogenation, 2-substituted hydroquinones in isolated, purified yields of about 50% based on 1,4-benzoquinone. The product hydroquinones have potential use as precursors to poly(arylene ether) and related aromatic polymers.

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1. Introduction

Alkylated hydroquinones and benzoquinones are found in nature and can have important cytotoxic and antioxidant activities.^{1,2} Hydroquinones are also important constituents of aromatic polymers such as poly(arylene ether)s and polyesters.^{3–5} Traditional synthetic approaches to alkylated hydroquinones include Friedel Crafts and free-radical alkylations as well as oxidation of substituted phenols.^{6–8} While procedurally simple, these methods often afford low yields or complex mixtures of products.

Trialkylboranes, conveniently generated by alkene hydroboration, can transfer one alkyl group to 1,4-benzoquinone to afford alkylated hydroquinones,⁹ usually in the presence of dioxygen.¹⁰ Either primary or secondary alkyl groups may be transferred, and the method tolerates functional groups that are compatible with BH₃ (halogens, esters, ethers, and nitriles).¹⁰ Although overall yields in these reactions are usually high, there are three frustrating complications. First, only one alkyl group from the trialkylborane is transferred, thereby wasting two equivalents of the starting alkene. Second, the borinic acid byproduct (R₂BOH) is difficult to separate from the desired hydroquinone. When R is relatively small (i.e., C₆ or less), the borinic acid can be removed by steam distillation, but

with larger R groups, researchers have resorted to derivatizing the hydroquinone to enable a separation.¹⁰ Third, alkene hydroboration with BH₃ (or with BH₃·SMe₂) is not highly regioselective, especially for alkenes having electron-withdrawing substituents near the double bond.¹¹ Although the initial hydroboration may afford mostly primary borane, the higher migratory aptitude of secondary radicals¹² can lead to significant contamination by the branched alkyl group in the hydroquinone,¹³ and then recrystallization is needed to obtain a pure regioisomer.

Recent advances in the preparation of organoboranes have partly alleviated these problems. Using catecholborane instead of BH₃ should, in principle, eliminate the problem of wasting two thirds of the alkene.¹⁴ *B*-Alkylcatecholboranes derived from various unfunctionalized alkenes will transfer a primary or secondary alkyl group to 1,4-benzoquinone. A recently reported method of preparing *B*-alkylcatecholboranes uses catecholborane in the presence of *N,N*-dimethylacetamide (DMAC), however this method has about the same regioselectivity for simple terminal alkenes as one would obtain using BH₃.¹⁵ Moreover, the optimized conditions for alkyl transfer to 1,4-benzoquinone requires a twofold excess of the *B*-alkylcatecholborane, ostensibly to outpace the natural tendency of the alkylated hydroquinone product to reduce the 1,4-benzoquinone reactant *in situ*. In this case the product hydroquinone must be separated from by-product catechol derivatives, likely including catecholboronic acid, *o*-C₆H₄O₂BOH.^{14,16} In preliminary experiments we found these kinds of separations difficult and inefficient.

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The challenge of product isolation in these procedures is not to be underestimated. Renaud developed a tetrahydroisoquinoline-derived catecholborane that facilitated removal of the byproducts by acidic aqueous extraction upon workup, however the needed catechol derivative is not commercially available and the overall procedure is complicated.¹⁶ Cole and co-workers generated trialkylboranes having the formula RBMe₂, which transfer primary and secondary alkyl groups to benzoquinone in strong preference to the methyl groups.¹⁷ However, preparing those trialkylboranes requires hydroboration with HBCl₂ (generated *in situ* from HSiEt₃ and BCl₃) followed by substitution of the BCl₂ moiety with MeMgBr, a pathway that excludes most other functional groups because of reagent incompatibilities.¹⁸ In another recent advance, alkyl- and arylboronic acids were combined with 1,4-benzoquinone to give 2-substituted 1,4-benzoquinones in moderate to high yields.¹⁹ Boronic acids are not always the most conveniently prepared synthetic intermediates.

In the course of our ongoing work on functionalized aromatic polymers we wanted to develop a general synthetic method for monosubstituted hydroquinones that would start with selective anti-Markovnikov hydroboration of an allyl ether and then transfer the 3-alkoxypropyl group to 1,4-benzoquinone. Because allyl ethers are readily prepared by Williamson synthesis, such a method would give us rapid access to a wide range of functional 2-substituted hydroquinone derivatives.

Preliminary efforts using BH₃·SMe₂ and catecholborane, with allyl ethyl ether as the substrate, afforded poor yields of the desired 2-(3-ethoxypropyl)hydroquinone. We then thought to use pinacolborane, which is not only more stable than catecholborane²⁰ but might also afford better regioselectivity because of its greater steric bulk and lower overall electrophilicity. However, the utility of *B*-alkylpinacolboranes in radical-transfer processes has met with mixed results. In particular, alkyl transfer to 1,4-benzoquinone was shown to be quite sluggish, even in the presence of K₂S₂O₈ and AgNO₃.¹⁹ On the other hand, a related fluorination with Select-Fluor™ showed better efficiency in the presence of CF₃COOH (TFA). We reasoned that TFA might facilitate the desired alkyl transfer to 1,4-benzoquinone as well. Such a procedure under oxidizing conditions (K₂S₂O₈, AgNO₃, and TFA) would ideally give an intermediate 2-substituted 1,4-benzoquinone, which we could then reduce to the corresponding hydroquinone derivative by catalytic hydrogenation, possibly with minimal workup between steps, thereby approaching one-pot efficiency. We now describe our efforts to explore these possibilities.

2. Results and discussion

Our efforts in the area of functionalized aromatic polymers have led us to develop a general synthetic approach to monosubstituted hydroquinones starting with anti-Markovnikov hydroboration of an allyl ether as the origin of the substituent that is then transferred from boron to 1,4-benzoquinone in a free-radical process. Like others before us, we started with BH₃·SMe₂ because of its simplicity and low cost. Even though we knew we would lose two thirds of our alkene to byproducts, we wanted to ensure that we could reproduce the results of others with our own hands. Table 1 shows the results of these preliminary studies. Yields obtained with 1-hexene and 1-octene (**1a** and **1b**, entries 1 and 2, respectively) are for purified products and are consistent with crude yields previously reported.¹³ Cyclooctene (**1c**, entry 3) gives a higher yield, possibly due to the enhanced migratory aptitude of the secondary alkyl group.¹²

Allyl ethers however, gave disappointing results (**1d-f**, entries 4–6). While a yield of 30% might seem tolerable, one must recall that this yield is based on 1,4-benzoquinone, whereas the allyl

ethers are the more precious of the two main reactants. Yields based on the allyl ethers are only about one third of the yields based on benzoquinone because only one alkyl group of the trialkylborane intermediate is transferred.

One factor in the low yields obtained for **2d-f** could be the low regioselectivity for hydroboration of allyl ethers noted by Brown and co-workers. Rather than question or repeat their work in this area, we moved on different hydroboration reagents. Even if we had obtained better yields for **2d-f**, the necessity of removing the byproduct borinic acid (R₂BOH) by steam distillation would tend to limit the range of useable allyl ethers. Moreover there is still the issue of wasting two-thirds of the alkene reactant.

We next explored monohydroborating agents and their use in generating substituted hydroquinones. As noted above, haloboranes such as HBCl₂ were ruled out entirely because they form strong complexes with ethers. Table 2 shows the results of our studies using catecholborane and Wilkinson's catalyst, (Ph₃P)₃RhCl, to effect hydroboration of four alkene substrates, followed by reductive alkyl transfer from the alkylboron intermediate to 1,4-benzoquinone. Yields are somewhat improved relative to those shown in Table 1, but "atom economy" with respect to the alkene is still low (2 equiv of *B*-alkylcatecholborane is needed), and the chromatographic separation of the product from catecholboronic acid and other by-products required large volumes of eluting solvents. Importantly, using one of our most urgently desired substrates, allyl phenyl ether (**1g**), the initial hydroboration was extremely sluggish and unpredictable, and in four attempts with the typical adjustments to conditions and isolation procedures, we obtained no yield of the corresponding 3-phenoxypropyl-1,4-hydroquinone (**2g**) whatsoever. Analysis of the reaction mixture by NMR spectroscopy after the initial hydroboration step revealed mostly unreacted allyl phenyl ether – an unacceptable result for us.

Still hoping to conserve alkene starting materials and improve the scope of our method, we switched to hydroboration with pinacolborane, which gives selective anti-Markovnikov addition to terminal alkenes using Wilkinson's catalyst.²⁰ Using 1-hexene (**1a**) for initial screening (Table 3), Rh-catalyzed hydroboration succeeded either in THF or dichloromethane solution, but the subsequent alkylation of benzoquinone entirely failed using aqueous THF (entry 1). Slightly more promising results for the alkylation step were obtained using a water-dichloromethane biphasic mixture (entry 5), but the reaction still afforded a very poor yield. Others have also found that alkyl transfer from *B*-alkylpinacolboranes to 1,4-benzoquinone is sluggish,¹⁹ so based on related findings²¹ in the area of fluorinations of *B*-alkylpinacolboranes, we reasoned that TFA might help facilitate alkyl transfer (entry 4). In contrast to that prior work, we found that TFA alone, rather than 4:1 TFA:H₃PO₄, gave the highest yields. Longer reaction time resulted in no improvement, so we considered the reaction to be optimized at the yields shown in Table 3. The final hydrogenation is not yield-limiting, as we optimized hydrogenation conditions separately.

Next we extended our method to allyl ethers (Table 3, entries 5–11). Variations in reaction time, proportions of reagents, etc. were explored, but isolated yields were reliably close to about 50% for the 2-alkylated hydroquinones after chromatographic purification. When we started with allyl 4-bromophenyl ether (**1h**, R = 4-C₆H₄Br), ¹H NMR spectroscopic analysis of the chromatographically purified product showed contamination with about 30% of the debrominated product (**2g**, R = C₆H₅), not a surprising result for a sequence that includes a noble-metal-catalyzed hydrogenation.²² We found, however, that the 3-aryloxypropyl-substituted 1,4-benzoquinones could be isolated (ca. 73% for R = C₆H₅; 60% for R = 4-C₆H₄Br). They are not especially stable, but reduction of the benzoquinone derivative bearing the pendant 4-bromophenyl group was effected cleanly using dissolving zinc in about 90%

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