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First Unambiguous Characterization of a Novel RO-BH$_2$ Intermediate by $^1\mathrm{H}\{^{11}\mathrm{B}\}$ and $^1\mathrm{H}\{^{13}\mathrm{C},^{11}\mathrm{B}\}$ NMR Spectroscopy. Proof of Boron−Carbonyl Interaction through Innovative Use of NMR Techniques

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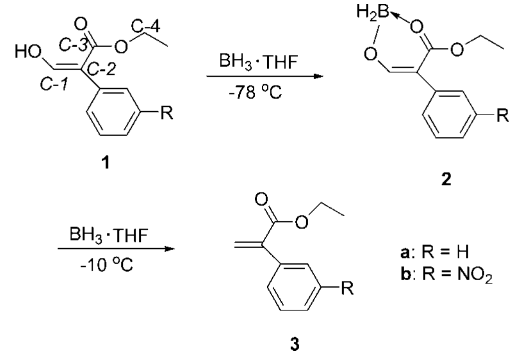
Summary: An unusual reduction of the aryl-substituted 3-hydroxyacrylic acid ester **1** *by BH$_3$ results in the propenoic acid ethyl ester* **3**. *We were able to prove the presence of an intermediate* **2** *containing a cyclic O-BH$_2$ ← O=C< moiety in* **2** *by using $^1H-^{11}B$ and $^1H-^{13}C\{^{11}B\}$ NMR correlation experiments.*

We have found that the aryl-substituted 3-hydroxyacrylic acid ester **1** can be reduced to propenoic acid ethyl ester **3** by using BH$_3$·THF (Scheme 1). This transformation was used as part of the synthesis of 2-(6-methoxy-2-naphthyl)propenoic acid, a valuable precursor for the synthesis of (*S*)-naproxen, starting from commercially available 6-methoxy-2-napthaldehyde.[1]

While hydroboration of C=C double bonds or reduction of carbonyl groups by boranes to alcohols are very common,[2] the reduction of an enol functional group to an olefin is unusual. In order to better understand the selectivity of the reaction, we embarked on a study of its mechanism by NMR spectroscopy. In the course of that study we focused our attention on the characterization of the borane-enol adduct formed in the first step of the reaction. Reaction of BH$_3$·THF with hydroxy groups is well documented and widely believed to yield species containing an O-BH$_2$ functionality.[3,4] Coordination of nitrogen stabilizes such species, and a few cases have been reported where such compounds were characterized. For example, ^{11}B NMR chemical shift arguments, ^{11}B NMR multiplicities, and IR stretching frequencies have been used to show that stable compounds comprising a cyclic O-BH$_2$ ← N structure are formed when BH$_3$·THF reacts with 8-hydroxyquinoline derivatives.[3,5] Equivalent five- and six-membered rings comprising an O-BH$_2$ ← O unit, where the BH$_2$ group is stabilized by the weaker interaction with an oxygen atom of a carbonyl group, have been proposed as intermediates,[6] but so far none of these proposed structures has been verified by spectroscopy. In this paper we report on the first full characterization of an intermediate **2** using NMR spectral through-bond correlation experiments to prove the presence of a cyclic O-BH$_2$ ← OC unit.

Scheme 1. Reaction of Substituted 3-Hydroxyacrylic Acid Ester 1 with BH$_3$



When a mixture of **1a** and 2 equiv of BH$_3$·THF is prepared at −78 °C and allowed to warm to near 0 °C, the enolic proton NMR signal around 12 ppm disappears over the course of several hours. Simultaneously the doublet due to H-1 of **1a** at 7.55 ppm is replaced by a singlet at 8.05 ppm, and a new set of ethoxy hydrogen signals appears. A new singlet at 4.62 ppm assigned to dissolved dihydrogen gas[7] is observed as well. Additional signals due to small amounts of olefin product **3a** and excess BH$_3$ are also present at this point. The data indicate that the hydroxy group of **1a** reacts with BH$_3$ with loss of hydrogen (Figure 1). Similar results are obtained with the *m*-nitro derivative **1b**, except that appearance of **2b** takes somewhat longer than **2a**. If ^{11}B decoupling is applied, the broad multiplet due to BH$_3$ sharpens considerably. In addition a singlet is observed at 3.45 ppm, which had otherwise been completely been obscured by the THF solvent signal. This signal appears to belong to a BH$_x$ group and grows with the other new signals mentioned above. From careful integration of that signal of a sample prepared from **1b** with BH$_3$·THF-d_8 we obtained a value of 1.7 relative to C(1)-H of **2b**. Considering that only 80% of all boron atoms belong to the decoupled isotope ^{11}B, this value is in agreement with a BH$_2$ group. ^{11}B NMR spectra also show a decrease of the quartet due to BH$_3$ as well as a new broad signal at 9 ppm. This signal initially exhibits a fine structure consistent with a triplet indicative of a BH$_2$ group. The observed chemical shifts are indicative of tetravalent boron.[8]

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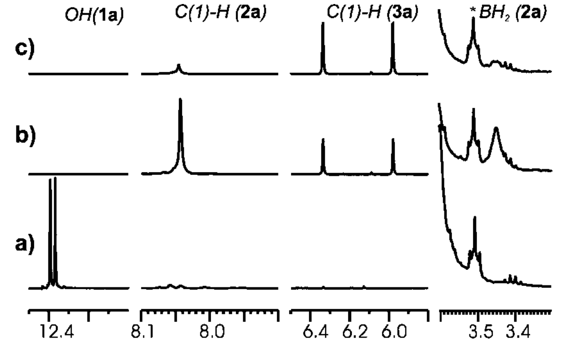

Figure 1. Reaction of **1a** with 1.8 equiv of $BH_3 \cdot THF$ followed by $^1H\{^{11}B\}$ NMR. (a) Initial spectrum at –50 °C; (b) after 5 h at −5 °C; (c) sample after 2 days in a refrigerator. ^{13}C satellite peaks of THF are marked with *.

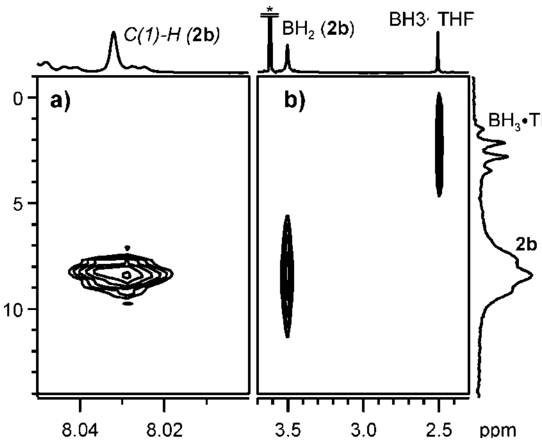

Figure 2. $^1H\{^{11}B\}$ correlations of a reaction mixture of **1b** and $BH_3 \cdot THF\text{-}d_8$ at 20 °C: (a) C(1)-H region of long-range $^1H\{^{11}B\}$ HMQC (mixing time 40 ms); (b) BH_2 region of one-bond $^1H\{^{11}B\}$ HSQC (mixing time 1.73 ms).

$^1H\{^{11}B\}$ HSQC spectra of **2** (transfer time τ =1.7 ms) exhibit a cross-peak between the BH_2 protons and the boron signal of **2** as expected for a one-bond proton−boron coupling. If τ is increased, an additional cross-peak is observed for **2** correlating C(1)-H with the boron signal at 9 ppm. This is consistent with a three -bond coupling between C(1)-H of **2** and the BH_2 moiety. Similar results are obtained using HMQC experiments (Figure 2). These results prove that BH_3 reacts with the enolic oxygen of **1** to form H_2 and a C(*1*)-O-BH_2 unit. However, no information is obtained as to whether the tetravalence of the boron in **2** arises from binding of an oxygen of a THF solvent molecule or by formation of a six-membered ring involving the C(3) carbonyl group.

One of the most powerful methods for obtaining connectivity information in small molecules is $^1H\{^{13}C\}$ HMBC spectroscopy. A $^1H\{^{13}C\}$ HMBC spectrum of **2a** shows correlations of both C(1)-*H* and C(4)-*H* to the carbonyl carbon *C*(*3*) as expected for the structure proposed. No correlation was observed for the BH_2 proton at 3.45 ppm. Such a negative result may be due to the fact that without decoupling of ^{11}B any magnetization of the BH_x proton will decay too fast due to scalar relaxation of the second kind to exhibit correlations in a HMBC spectrum. Encouraged by the extreme sharpening of the BH_n proton NMR signals, we repeated the HMBC experiment on an instrument equipped with a broadband triple resonance probe ($^1H/^{13}C/X$). That allowed us to apply ^{11}B decoupling throughout the experiment. Under those conditions two cross-peaks were observed for the BH_2 proton (3.45 ppm). One cross-peak was with the enolic carbon (C-1); the other with the carbonyl carbon *C*(*4*) (Figure 3). The experiment therefore proves that a cyclic structure is formed with the boron bound to both the enolic oxygen C(*1*)-O and the carbonyl oxygen C(*3*)═O. Intramolecular coordination of the carbonyl group also explains the relative stability of the intermediate **2**.

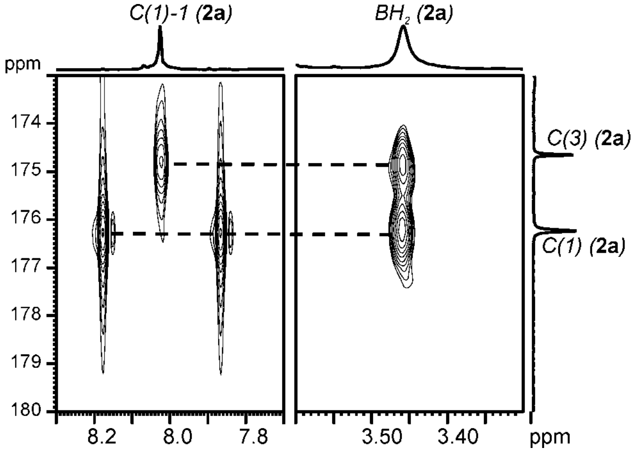

Figure 3. ^{11}B decoupled $^1H\{^{13}C\}$ HMBC spectrum of a reaction mixture of **1a** and $BH_3 \cdot THF$ at −5 °C. Shown are the correlations of the C(1)-H (left) and BH_2 (right) protons of **2a** with the carbonyl (C3) and C(1) carbon atoms.

If the mixture is left for longer time, at around 0 °C or room temperature a further increase in the amount of olefin **3** is observed at the expense of the intermediate **2** (Figure 1c). Simultaneously a signal at 19 ppm appears in the ^{11}B NMR spectrum, indicative of a $B(OR)_3$ species. In addition, the signal due to excess BH_3 also continues to decrease in intensity. These findings indicate that olefin **3** forms by cleavage of the C(1)−oxygen bond in the absence of water or other protic solvents. In addition, it appears that a second equivalent of BH_3 is required to form olefin **3** from the intermediate **2**. No olefin is formed once all BH_3 is used up. This assumption was verified by repeating the reaction using only 0.5 equiv of BH_3, which showed very clearly that olefin formation ceases once all BH_3 has been consumed. Another piece of evidence was obtained when BD_3 was used as reactant. NMR spectra of the olefin **3a** formed under those conditions showed that the deuterium was incorporated in the cis and trans positions in equal amounts, which is more likely to occur in an intermolecular rather than intramolecular hydrogen transfer step. Further details on the mechanism of this part of the reaction remain under investigation.

In summary, we have shown that reduction of enol **1** occurs by way of an intermediate **2**, in which the boron is bound to both the enolic oxygen atom and the β-carbonyl group in a cyclic manner. By using through-bond NMR correlation experiments to and across ^{11}B nuclei we were able for the first time to fully characterize an oxygen-stabilized O-$BH_2 \leftarrow$ OC moiety.

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Supporting Information Available: ^1H, ^{13}C. and ^{11}B NMR spectra of **2a** and **2b** and other related information. This material is available free of charge via the Internet at http://pubs.acs.org.

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