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Deuteration of alkenes with $NaBD_4$/AcOD in presence of Pd on carbon

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† Presented at the title, place, and date.

Received: date; Accepted: date; Published: date

Abstract: Activated alkenes such as cinnamates and chalcones can easily be converted to 2,3-dideuterio-arylpropionates and dideuteriochalcones, respectively, by the action of $NaBD_4$, AcOD in the presence of Pd on carbon. Toluene or benzene was used as solvent. It was shown that Pd on carbon was necessary for the reaction to proceed. Deuterium addition experiments were also carried out with $NaBD_4$, AcOD, D_2O in the presence of Pd on carbon

Keywords: deuterium addition, *in situ* deuterium production, sodium borodeuteride

1. Introduction

A number of years ago, the hydrogenation of an alkene using externally added H_2 in the presence of a palladium-on-carbon catalyst led to a small fire in the laboratory. Just after, we started looking for a method of developing hydrogen in situ and settled on a method disseminated by Cordes et al., using a combination of $NaBH_4$ and CH_3CO_2H [1,2]. When run in the presence of Pd/C, this reaction proved to be a very effective method of hydrogenating alkenes. Indeed, we found that when the reaction is monitored carefully, the hydrogenation proceeds without *O*- and *N*-debenzylation [3]. In the following, the authors detail the outcome of the reaction carried out with the deuterated reagents $NaBD_4$-CH_3CO_2D [4].

2. Materials and Methods

3.1. General remarks

Melting points were measured on a Stuart SMP 10 melting point apparatus and are uncorrected. Infrared spectra were measured with a Thermo/Nicolet Nexus 470 FT-IR ESP spectrometer and a Perkin Elmer Spectrum Two spectrometer. ^1H and ^{13}C NMR spectra were recorded with a Varian 400 NMR spectrometer (1H at 395.7 MHz, ^{13}C at 100.5 MHz). The assignments of the carbon signals were aided by DEPT 90 and DEPT 135 experiments (DEPT = Distortionless Enhancement by Polarisation Transfer). The chemical shifts are relative to TMS (solvent $CDCl_3$, unless otherwise noted). Mass spectra were measured with a JMS-01-SG-2 spectrometer, and with an Agilent QTOF 6540 UHD. Column chromatography, where necessary, was performed on recycled silica gel (S, 0.063 mm – 0.1 mm, Riedel de Haen and Merck grade 9385).

3.2. Starting materials

Acetic-d^1 (Aldrich), deuterium oxide (D_2O, Aldrich), sodium borodeuteride ($NaBD_4$, Aldrich) and palladium on carbon (Pd/C, 5w%, Aldich) were acquired commercially. The alkenes were prepared

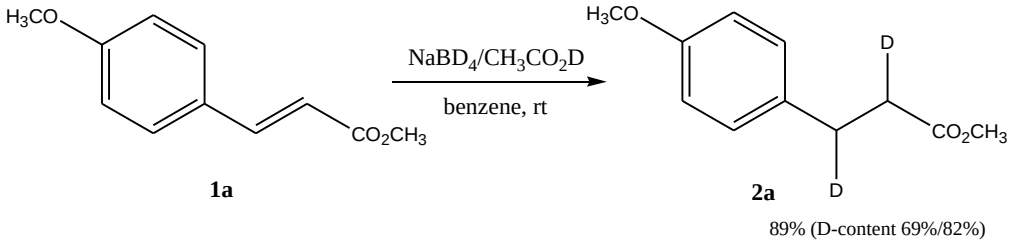
by Wittig olefination of the corresponding, commercially available benzaldehydes with methyl carboxymethylidenetriphenylphosphorane in the case of the methyl cinnamates. Cinnamides were prepared by Appel-type amidation of cinnamic acids [5], cinnamates other than methyl cinnamates by Appel-type esterification [5]. Cinnamic acids were either commercially available or were prepared by a one-pot Wittig olefination – ester hydrolysis procedure [6].

3.2. General procedures

Methyl 2,3-D_2-3-(4-methoxyphenyl)propionate. - To methyl 4-methoxycinnamate (**1a**, 270 mg, 1.4 mmol) in benzene (15 mL) was added Pd/C (140 mg, 10 w%), $NaBD_4$ (250 mg), then acetic acid-D (200 mg) and the mixture was stirred for 12h. Then, acetic acid-D (100 mg) is added again and the mixture is stirred for another 12h at rt. Then, three drops of D_2O are added, the mixture is filtered and the filtrate is poured into H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 phase is dried, concentrated and separated by column chromatography (CH_2Cl_2) to give methyl 2,3-D_2-(4-methoxyphenyl)propionate (**2a**, 242 mg, 89%, D content 69/82%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.59 (1H, m), 2.88 (1H, m), 3.66 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 6.83 (2H, d, ^3J = 8.8 Hz), 7.11 (2H, d, ^3J = 8.8 Hz); ^{13}C NMR (100.5 MHz) δ = 29.9 (m, CHD), 35.7 (m, CHD), 51.6 (OCH_3), 55.2 (OCH_3), 113.9 (2C, CH), 129.2 (2C, CH), 132.5 (C_{quat}), 158.0 (C_{quat}), 173.4 (C_{quat}, CO).

4. Results and Discussion

Deuterated compounds are interesting because of their utility in analytic spectroscopy such as standards in mass spectrometry [7]. Furthermore due to their oftentimes slower metabolic rates, deuterated molecules of pharmaceutical interest may have longer half-lives *in vivo* and an altered toxicity profile as compared to their ^{1}H-analogs [8,9]. A handful of deuterated pharmaceutics are in clinical trials [10,11], with deutetrabenazine D already on the market to treat chorea associated with Huntington's disease [12,13]. There are a number of ways to deuterate compounds [cf., ref. 14]. One such way is the deuteration of alkenes [15,16], eg., the addition of deuterium to a double bond. In former times, diverse methods were devised to produce deuterium. They included the fractional distillation of liquid hydrogen (H_2 bp. -252.9 ˚C; D_2 bp. –249.5 ˚C), the pyrolysis of UD_3 [17], the reaction of D_2O with sodium, iron or magnesium [18], and the large-scale electrolysis of D_2O [19]. In recent times, it has been seen that a hydrogen atmosphere stirred over D_2O can exchange to a deuterium atmosphere (over DOH) in presence of a palladium(0) catalyst (eg., in the presence of Pd/C) [16]. A source of deuterium presents itself also in the system Na-dispersion / EtOD-d^1 in ether [15].



Scheme 1. Addition of *in situ* prepared deuterium to methyl 4-methoxycinnamate (**1a**).

In the following, deuterium was to be produced by the reaction of sodium borodeuteride ($NaBD_4$) with acetic acid-d^1, which subsequently would transform an activated alkene in the presence of Pd/C to an α,β-dideuteroalkane. Indeed, this was found to be the case and a number of acrylates, acrylamides and enones could be reacted to the corresponding dideuterated compounds (Table 1). For compounds **5a/b**, an inverse addition of the starting material to a prepared mixture of $NaBD_4$-CH_3CO_2D-Pd/C in benzene was carried out. **4** is the product of the deuteration of 1-(3-benzyloxy-4-methoxyphenyl)-2-*p*-tolylethene, where due to the long reaction time chosen (48h), the compound was *O*-debenzylated, also. That deuterium addition could also be carried out without concommittant

O- or *N*-debenzylation [3] was shown in the products **3a** and **5b**. In the case of **5b**, D_2O was added immediately after the addition of the substrate to the mixture of $NaBD_4$, CH_3CO_2D, Pd/C in benzene. The reaction was worked up 30 min. after the addition of D_2O. The deuterium content in all products was measured by ^1H NMR spectroscopy.

In this general set-up, $NaBD_4$ reacts with acetic acid-d[1] to give sodium acetate, deuterium (D_2) and deuteroborane, which is in equilibrium with deuterated diborane. Deuterated diborane would be able to react with deuterated water (D_2O) to give deuterated boric acid and another 6 equiv. of deuterium (D_2). From these equations, one can gather two insights: a.) one could imagine that as deuterium and deuteroborane form in equal amounts in the first step, a reaction mechanism involving deuteroborane exclusively could also be possible (see below). b.) in absence of D_2O, only 1 equiv. D_2 of 7 possible equiv. D_2 would be used. In all the reactions described above, D_2O was added at the termination of the reaction, which seems sensible in retrospect as any residual $NaBD_4$ would lead to the creation of HD and BD_xH_y upon addition of H_2O itself.

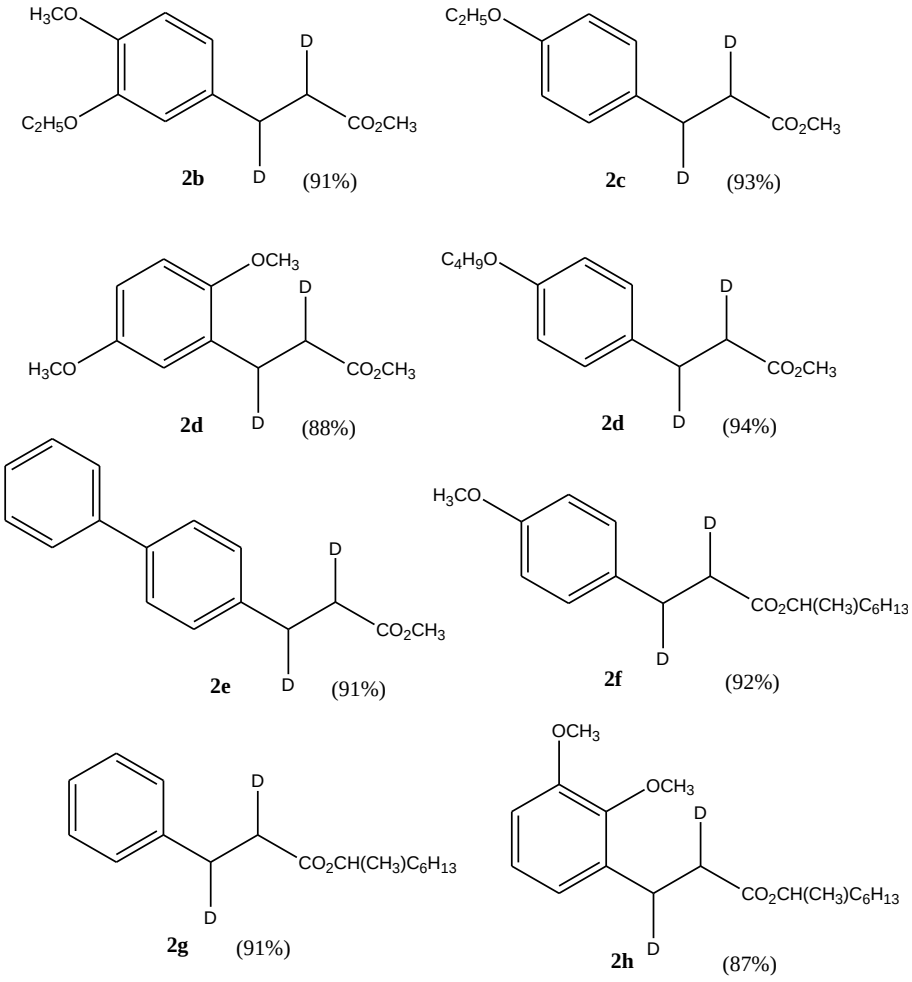


Table 1. Typical products prepared by deuterium addition to the respective alkene starting materials ($NaBD_4$, CH_3CO_2D, Pd/C, benzene or $NaBD_4$, CH_3CO_2D, D_2O, Pd/C, benzene).

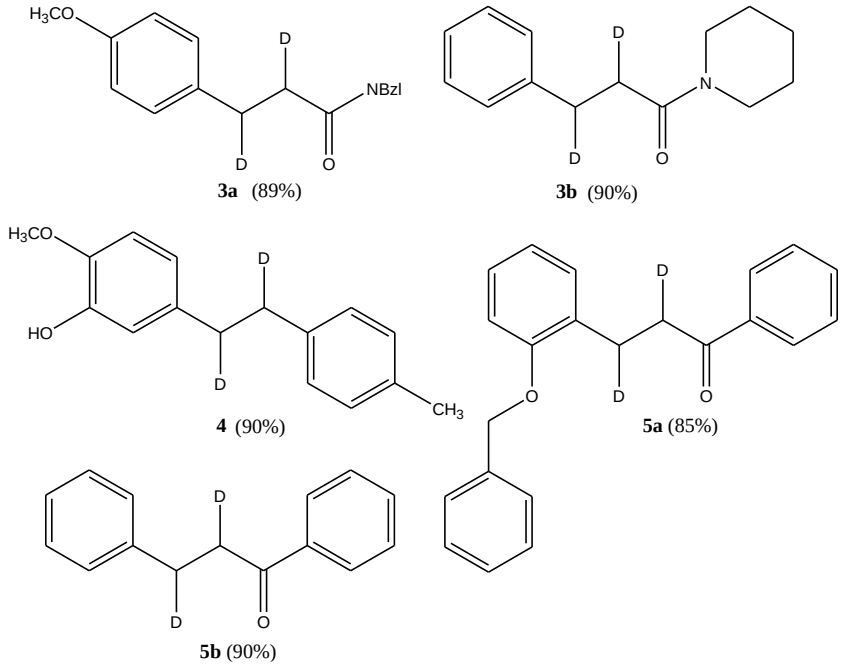
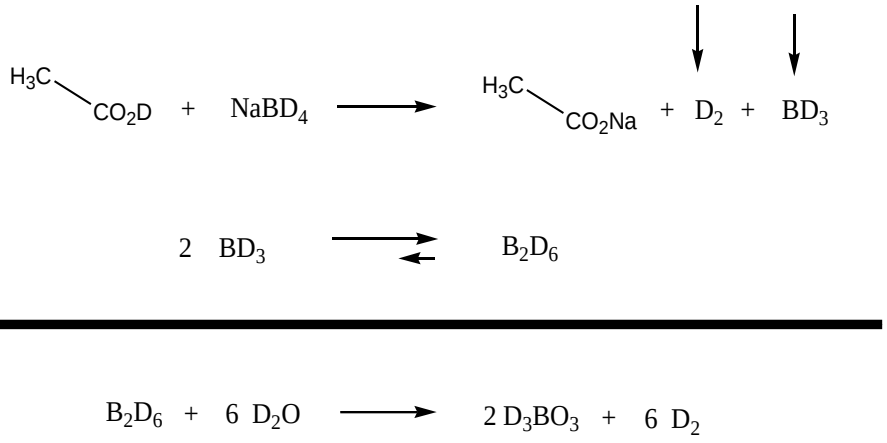


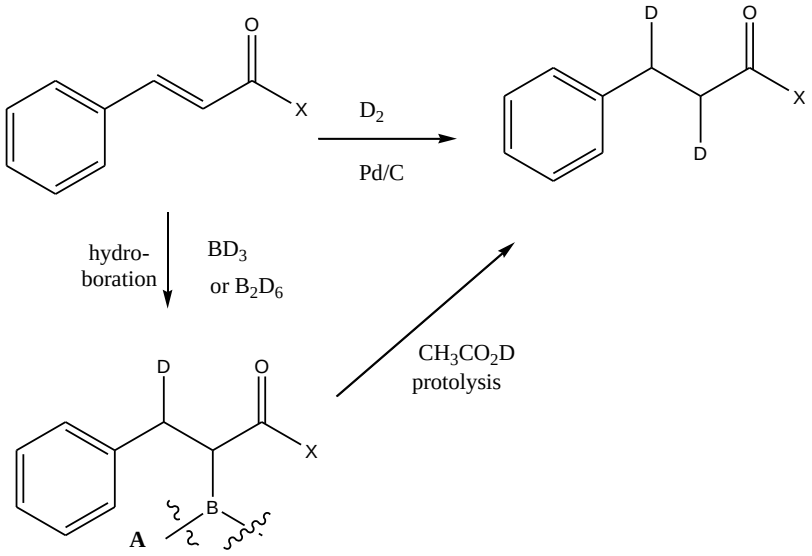
Table 1. (continued)



Scheme 2. Reaction of sodium borodeuteride with acetic acid – d[1]

Two potential main pathways could be envisaged for the deuteration of alkenes under the reaction conditions described. One would be the deuteroboration of the alkene with deuterated borane, with subsequent protolysis. This reaction would proceed in absence of Pd/C, also. In order to ascertain the pathway of the reaction, methyl 4-methoxycinnamate was reacted with $NaBH_4$-CH_3CO_2H in benzene. Here, the hydrogenated product methyl 4-methoxypropionate was obtained in 10% yield, only,signalizing that the hydroboration-protolysis is only a minor pathway in the transformation under the conditions. Separate experiments of adding H_2O (or D_2O) immediately after preparing the reaction system $NaBH_4$-CH_3CO_2H ($NaBD_4$-CH_3CO_2D) increased the evolution of H_2 (D_2) significantly and in presence of Pd/C facilitated the transformation to the α,β-dideuterated products appreciably. Lastly, **5a** was produced in this fashion (see above).

Two concurring mechanisms are possible:



Scheme 3. Two potential pathways to the dideuterated product when using the reaction system $NaBD_4$, CH_3CO_2D, Pd/C.

5. Conclusion

In conclusion, it is possible to add deuterium to alkenes using the reaction system $NaBD_4$, CH_3CO_2D, and cat. Pd/C. The addition of D_2O at an early stage of the experiment enhances the reaction, most likely through the formation of further deuterium by converting *in situ* formed deuterodiborane, making it possible to stop the reaction after 30-40 min. at rt. In absence of Pd/C, only little hydrogenated product is formed with $NaBH_4$ – acetic acid, clearly indicating that a potential hydro(deutero)boration – protolysis mechanism is only a minor pathway.

Author Contributions: Conceptualization, supervision, investigation, writing—original draft preparation, T.T.; investigation, F.A., Han. A., Hal. A., A. H. and Ab. H. in equal measure.

Conflicts of Interest: The authors declare no conflict of interest.

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