Reduction of α,β-unsaturated carbonyl compounds with sodium borohydride in the diethyl ether/methanol/pentafluorophenol solvent system. Use of *N,N,N',N'*-tetramethylethylenediamine and 1-hexene as borane scavengers

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Abstract

Pentafluorophenol acts as an efficient proton source for sodium borohydride reductions in diethyl ether containing methanol. This system allows for the regioselective reduction of α,β-unsaturated carbonyl compounds to the corresponding allylic alcohols in high yield. Use of either 1-hexene or *N,N,N',N'*-tetramethylethylenediamine as borane scavengers moderately improved the regioselectivity of this reaction. Fortunately, sodium trispentafluorophenoxyborohydride, generated *in situ*, gave regiospecific 1,2-reduction of α,β-unsaturated carbonyl compounds.

Introduction

It is well known that the regiospecific reduction of α,β-unsaturated carbonyl compounds to the allylic alcohols is still a challenging task to perform [1]. $NaBH_4$ and $LiAlH_4$ have been shown to give 1,2- and/or 1,4-reduction products depending on the type and substituents of the substrate [2]. A number of new hydride reducing agents have been developed to give mainly 1,2-reduction products, but the applicability of these reagents depends on the structure of a particular substrate [3]. Reagents, such as $NaCNBH_3$ [4], 9-borabicyclo[3.3.1]nonane (9-BBN) and diisobutylaluminum hydride (DIBAH) are either toxic or require anhydrous and inert atmosphere conditions.

The most reliable reagents, so far, for the 1,2-reduction of α,β-unsaturated carbonyl compounds are aminoborohydrides [5] and sodium borohydride $CeCl_3$ in methanol [6]. However, a large excess of sodium borohydride is required in the latter method. It has been shown that the acidity of methanol is enhanced in the presence of $CeCl_3$ and this acidic alcohol system efficiently protonates the α,β-unsaturated carbonyl compounds to facilitate their reductions to the corresponding allylic alcohols [6]. A major drawback of this reaction is that cerium is highly toxic and its efficient recycling is cumbersome. We were interested in modifying the acidity of methanol using fluorinated alcohols and utilizing this mixed solvent system for the 1,2-reduction of α,β-unsaturated carbonyl compounds.

Results and discussion

For our initial study, we chose to look at the reduction of 2-cyclohexen-1-one. A 1 M diethyl ether solution of methanol and pentafluorophenol was used as the solvent system. In this study, two different modes of addition of $NaBH_4$ were investigated: first, normal addition where $NaBH_4$ was added to a solution of the substrate in the mixed solvent system. The second mode of addition was an inverse addition where pentafluorophenol was added to a mixture of the substrate, MeOH and $NaBH_4$ in Et_2O. The reactions were carried out for 1 h at 0 °C and the products were analyzed by capillary GC. The results are summarized in Table 1.

The results summarized in Table 1 show that when 1 M pentafluorophenol in diethyl ether was used as the solvent, considerable 1,4-reduction occurred. Inverse addition gave more 1,4-reduction relative to normal addition. We also noticed that the 1,2-selectivity increased with the amount of pentafluorophenol. The use of 2 equiv. of pentafluorophenol in 1 M methanol solution in diethyl ether gave 1,2-reduction in 80% yield. We speculate that borane (BH_3) was formed as an intermediate in these reductions and is most likely responsible for the 1,4-reduction product. Consequently, we used borane scavengers such as 1-hexene and *N,N,N',N'*-tetramethylethylenediamine [7] to scavenge

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TABLE 1. Reaction of 2-cyclohexen-1-one with sodium borohydride in a mixed solvent system in the presence of borane scavengers

Acid source (equiv.)	Normal addition	Inverse addition
	1,2:1,4	1,2:1,4
C_6F_5OH (1)	61:39	58:41
C_6F_5OH (2)	72:28	70:30
C_6F_5OH (3)	72:28	78:22
C_6F_5OH (2) + MeOH (1)	80:20	41:59
C_6F_5OH (1) + 1-hexene (1)	74:26	69:31
C_6F_5OH + TMEDA (0.5)	70:30	59:41

any borane formed during the reduction. However, the use of these additives improved the regioselectivity only marginally. Apparently, any borane formed is quenched rapidly by methanol under the reaction conditions. These results are also summarized in Table 1.

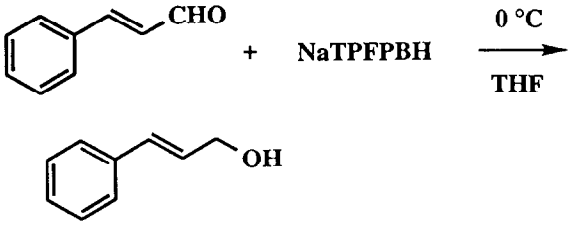
Reactions of NaTPFPBH with α,β-unsaturated aldehydes and ketones

Recently, we found that sodium borohydride reacts with 3 equiv. of pentafluorophenol to form sodium tris(pentafluorophenoxy)borohydride (NaTPFPBH) [eqn. (1)] [8]

$$NaBH_4 + 3C_6F_5OH \xrightarrow[\text{THF, 3h}]{0\ ^\circ C} NaBH(OC_6F_5)_3 + 3H_2\uparrow \quad (1)$$

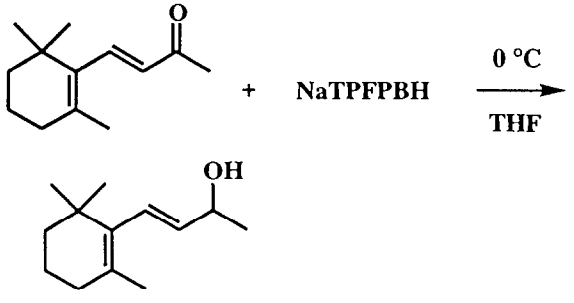
We studied the reaction of NaTPFPBH with representative α,β-unsaturated aldehydes and ketones as a possible route to allylic alcohols. The reactions were carried out for 1 h at 0 °C and the products were analyzed by capillary GC. The results are summarized in Table 2.

All of the α,β-unsaturated aldehydes and ketones examined underwent 1,2-reduction to yield the corresponding allylic alcohols. The α,β-unsaturated aldehyde *trans*-cinnamaldehyde upon reaction with NaTPFPBH yielded the allylic alcohol *trans*-cinnamyl alcohol [eqn. (2)].



(2)

The α,β-unsaturated terpene ketone β-ionone upon reaction with NaTPFPBH gave the corresponding allylic alcohol β-ionol [eqn. (3)]. Similarily, reduction of 2-cyclohexen-1-one with NaTPFPBH gave the allylic alcohol 2-cyclohexen-1-ol.



(3)

It appears that fluorinated alcohols can be used to increase the acidity of methanol. Utilization of this system described herein is widely applicable to the selective 1,2-reduction of α,β-unsaturated carbonyl compounds. The allylic alcohols formed in these processes are isolatable in both high yield and purity. NaTPFPBH showed selectivity towards 1,2-reductions in α,β-unsaturated aldehydes and ketones to yield the corresponding allylic alcohols. In comparison with other sodium and potassium borohydrides, which suffer from having four equivalent hydrides per molecule, NaTPFPBH has only one hydride per molecule [9]. Consequently, in the reduction process, different intermediates with different reactivities form for the sodium

TABLE 2. Reaction of sodium tris-pentafluorophenoxyborohydride with representative α,β-unsaturated aldehydes and ketones in tetrahydrofuran at 0 °C

Compound[a]	1,2-Reduction[b] (%)	Unreacted substrate[b] (%)
trans-Cinnamaldehyde	100	0
Myrtenal	100	0
β-Ionone	66	34
(*S*)-Carvone	52	48
2-Cyclohexen-1-one	61 (1)	38

[a]See general procedure for the reactions of (NaTPFPBH) with α,β-aldehydes and ketones described in the Experimental section. [b]Ratio of products determined by capillary GC analysis with internal standards. The number in the parenthesis indicates the percentage of 1,4-reduction product.

and potassium borohydrides, while the side product of NaTPFPBH, i.e. tris(pentafluorophenoxy)borane, is unreactive under the reaction conditions examined*. Sodium and potassium borohydrides have a very low solubility in common organic solvents such as THF and Et_2O [10]. The use of NaTPFPBH overcomes these problems associated with other alkali metal borohydrides. NaTPFPBH shows an excellent solubility in common organic solvents such as THF and Et_2O. NaTPFPBH can be readily prepared, in addition to being stable without requiring an equilibrium concentration of alkali metal hydride present. Since potassium triisopropoxyborohydride is no longer commercially available, NaTPFPBH is an attractive alternative for these selective reductions. We are actively exploring the use of other fluorinated alcohols as ways of increasing the acidity of alcohol solutions for the reduction of organic substrates.

Experimental

All operations were carried out under a nitrogen atmosphere unless otherwise specified. All glassware, syringes and needles were oven-dried and cooled under a nitrogen atmosphere. Tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone ketyl. Anhydrous ethyl ether (Et_2O) was purchased from Fisher and used directly. The compounds examined here are available from Aldrich Chemical Company and were used neat or in standardized solution as described below.

^{11}B NMR spectra were recorded with a Bruker ACF 250 MHz spectrometer. Chemical shifts were relative to $Et_2O \cdot BF_3$, with chemical shifts downfield from $Et_2O \cdot BF_3$ assigned positive. ^1H and ^{13}C NMR spectra were recorded with a Bruker ACF 250 MHz spectrometer. Chemical shifts are relative to Me_4Si. Capillary GC analyses were carried out on a Hewlett Packard 5890 chromatograph fitted with a 25 M Methylsilicone column and a 45 M Carbowax capillary column. All GC yields were determined by using a suitable internal standard and authentic mixtures.

General procedure for the reactions of 2-cyclohexen-1-one with sodium borohydride in a mixed solvent system in the presence of borane scavengers

The following procedure for the reduction of 2-cyclohexen-1-one is representative for the normal addition of $NaBH_4$ to a mixed solvent system containing Et_2O, pentafluorophenol as an acid source and *N,N,N',N'*-tetramethylethylenediamine as a borane scavenger. To an oven-dried 15 ml serum vial fitted with a septum and stirbar, 2-cyclohexen-1-one (97 μl, 1 mmol) was added and dissolved in Et_2O (1 ml). The reaction mixture was then cooled to 0 °C. Pentafluorophenol (0.368 g, 2 mmol) and *N,N,N',N'*-tetramethylethylenediamine (75 μl, 0.5 mmol) were added sequentially. The reaction mixture was allowed to stir for 5 min and $NaBH_4$ (0.038 g, 1 mmol) was then added to it. The reaction mixture was allowed to stir for 1 h at 0 °C. It was then quenched sequentially with H_2O (1 ml) and 3 M HCl (2 ml). The reaction products were extracted with Et_2O (5 ml), washed with 3 M NaOH (2 ml) and H_2O (2×2 ml) and dried over anhydrous $MgSO_4$. Capillary GC analysis of the organic fraction with internal standard on a 25 M Methylsilicone column showed the product distribution to be 70% 2-cyclohexen-1-ol as the 1,2-reduction product and 30% cyclohexanol as the 1,4-reduction product (see Table 1).

Synthesis of sodium tris(pentafluorophenoxy)borohydride at 0 °C in tetrahydrofuran

The following procedure is representative. An oven-dried 250 ml round-bottom flask, equipped with a magnetic stirring bar and septum, was charged with $NaBH_4$ (1.7 g, 45 mmol) and THF (10 ml) and cooled to 0 °C. A 3.0 M THF solution of pentafluorophenol (45 ml) was added dropwise via a double-ended needle over a period of 30 min and the reaction mixture stirred at 0 °C for 12 h to ensure complete reaction. The ^{11}B NMR spectrum of the reaction mixture showed a signal at δ 5.8 (d) ppm due to the quantitative formation of NaTPFPBH. Hydride analysis using a gas burette [11] showed that the reaction mixture was 1.0 M in hydride concentration. The reagent thus prepared was kept in an ampoule under nitrogen at 0 °C and no appreciable disproportionation could be detected even after 6 months.

General procedure for the reactions of NaTPFPBH with α,β-unsaturated aldehydes and ketones

The reduction of 2-cyclohexen-1-one is representative. To an oven-dried 15 ml serum vial fitted with a septum and stirbar was added 2-cyclohexen-1-one (1 mmol) dissolved in THF (1 ml) and cooled to 0 °C. NaTPFPBH in THF (1 ml, 1 mmol) was then added and the mixture stirred for 3 h at 0 °C. It was then quenched sequentially with H_2O (1 ml) and 3 M HCl (2 ml). The reaction products were extracted with Et_2O (5 ml), washed with 3 M NaOH (2 ml) and H_2O (2×2 ml), and dried over anhydrous $MgSO_4$. Capillary GC analysis of the organic fraction on a 25 M Methylsilicone column showed the product distribution to be essentially 2-cyclohexen-1-ol with a trace amount of unreacted 2-cyclohexen-1-one (see Table 2).

*The tris(pentafluorophenoxy)borane byproduct is easily and rapidly hydrolyzed with water and dilute hydrochloric acid.

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