Highly Selective Syntheses of Coniferyl and Sinapyl Alcohols

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(*E*)-Isomers of coniferyl and sinapyl alcohols were readily and cleanly prepared in excellent yields from commercially available coniferaldehyde and sinapaldehyde by sodium triacetoxyborohydride reduction in ethyl acetate. No 1,4-reduction products, always produced in prior methods, could be detected.

Keywords: *Coniferyl alcohol; sinapyl alcohol; monolignol; lignin; triacetoxyborohydride; dihydroconiferyl alcohol; coniferaldehyde; sinapaldehyde; regiospecific reduction*

INTRODUCTION

Coniferyl and sinapyl alcohols are utilized for various biochemical and chemical studies relating to lignans and lignins, for which they are the component monomers. Because of their relative simplicity and their value as a tool to approach lignin structure, synthetic lignins or dehydrogenation polymers (DHPs), made in vitro by oxidative polymerization of 4-hydroxycinnamyl alcohols, have been used extensively to model lignin biosynthesis and obtain information about lignin structure (Freudenberg and Hübner, 1952). Such investigations are hindered by poor accessibility to pure 4-hydroxycinnamyl alcohols.

A number of synthetic methods for 4-hydroxycinnamyl alcohols have been developed (Allen and Byers, 1949; Freudenberg and Hübner, 1952; Freudenberg and Swaleh, 1969; Quideau and Ralph, 1992; Ludley and Ralph, 1996). The alcohols were originally obtained from their corresponding cinnamates by lithium aluminum hydride reduction in moderate yield (Freudenberg and Swaleh, 1969). Recently, more selective reducing agents such as diisobutylaluminum hydride or its "ate-complex" have been used to improve selectivity and allow conversion of unprotected 4-hydroxycinnamates to alcohols (Newman et al., 1986; Quideau and Ralph, 1992). Other approaches to 4-hydroxycinnamyl alcohols have also been reported (Zanarotti, 1982; Steglich and Zechlin, 1978; Rothen and Schlosser, 1991; Daubresse et al., 1994). All of them suffer from either low yields, undesirable contaminants, or difficult to handle reagents. Normally, coniferyl or sinapyl alcohol prepared according to these methods is contaminated with various amounts of the saturated alcohol, which is hard to separate even by recrystallization. Now that the aldehydes are commercially available, their reductions provide the easiest way to prepare the hydroxycinnamyl alcohols. However, coniferyl or sinapyl alcohol prepared according to the recently described method (Ludley and Ralph, 1996), in which sodium borohydride ($NaBH_4$) was used as the reducing agent, is still contaminated with saturated alcohols. Here we report a facile and highly selective method to synthesize coniferyl or sinapyl alcohol from coniferaldehyde or sinapaldehyde by sodium triacetoxyborohydride [$NaBH(OAc)_3$] reduction in ethyl acetate in excellent yields. The method is simple and safe enough that nonchemists can readily make the requisite monolignols.

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EXPERIMENTAL PROCEDURES

Melting points are uncorrected. NMR spectra were run in acetone-d_6 on a Bruker AMX-360 instrument, operating at 360.13 MHz ^{1}H (90.55 MHz ^{13}C). The central solvent signal was used as internal reference (^{1}H, 2.04 ppm; ^{13}C, 29.80 ppm). Coniferaldehyde, sinapaldehyde, $NaBH_4$, and commercial $NaBH(OAc)_3$ were obtained from Aldrich and used directly. Ethyl acetate from J. T. Baker was of analytical grade. Petroleum ether is the 40−60 °C boiling fraction. GC used an SPB-1 column. Products obtained were identified by comparison of their NMR data with those published in the literature.

Preparation of Sodium Triacetoxyborohydride. Preparation from sodium borohydride in situ prior to reduction is our preferred method. To $NaBH_4$ (74 mg), suspended in ethyl acetate (15 mL) and cooled with an ice−water bath, was added glacial acetic acid (3.05 equiv) by syringe over ∼5 min. Stirring was continued for another 5 min until a clear solution was formed. The solution is the ready-to-use reducing agent. For large scale (3.5 g), the addition of acetic acid was performed dropwise over ∼30 min and stirring continued for a further 30 min.

Coniferyl Alcohol 2a. *(E)*-Coniferaldehyde **1a** (134 mg, 0.753 mmol) was added at room temperature to sodium triacetoxyborohydride (3.0 equiv) in ethyl acetate, prepared as above. The reaction was monitored by TLC (5% CH_3OH in CH_2Cl_2). TLC showed that the starting material completely disappeared in 7 h. However, the reaction mixture was kept overnight and then diluted with ethyl acetate and quenched with water (20 mL). The organic phase was separated, and the water fraction was extracted with ethyl acetate (2 × 20 mL). The combined ethyl acetate was washed with water (20 mL) and saturated NH_4Cl (20 mL) and dried over $MgSO_4$. Evaporation of the solvent gave a light yellow syrup that still contained acetic acid. The residual acetic acid was removed by coevaporation with ethanol. ^{1}H NMR and GC of this crude **2a** (132 mg, 97%) showed no detectable 1,4-reduction product (detectability limit < 0.05%). Crystallization from CH_2Cl_2/petroleum ether gave *(E)*-**2a** as pale yellow plates (95 mg, 70%), mp 77.2−77.9 °C [lit. (Freudenberg and Hübner, 1952) 74−76 °C; (Daubresse et al., 1994) 75−76 °C; (Quideau and Ralph, 1992) 77.9−78.6 °C]. For large scale preparation (5

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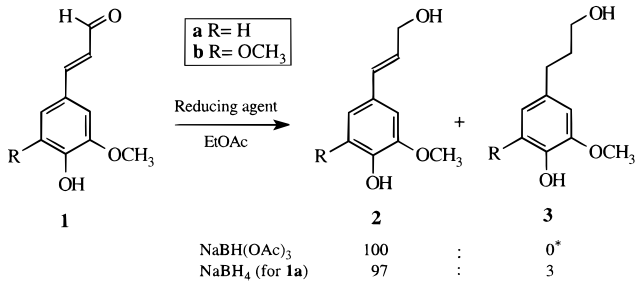

Figure 1. Reduction of coniferaldehyde **1a** and sinapaldehyde **1b**. * The ratio was measured by GC; **3a**,**b** were undetectable in products of $NaBH(OAc)_3$ reductions.

g), after addition of coniferaldehyde **1a**, the mixture was stirred overnight (~10 h) at room temperature. Workup as above afforded crude **2a** without any 1,4-reduction product detectable by GC. Crystallization from CH_2Cl_2/petroleum ether led to pure **2a** as pale yellow plates in 77% yield.

Reduction with Commercial Sodium Triacetoxyborohydride. The acetoxyborohydride reagent is available commercially but seems to function more slowly than the in situ-prepared reagent that is conveniently prepared as described above. Commercial $NaBH(OAc)_3$ (1.68 mmol, 3.0 equiv) was suspended in ethyl acetate (15 mL), and coniferaldehyde **1a** (100 mg, 0.56 mmol) was added. The mixture was stirred overnight when TLC showed that ~40% of the starting material remained. About 0.1 mL of acetic acid was added, and stirring was continued for 6 h, at which time TLC showed the reduction was done. Workup as above afforded crude **2a** (96 mg, 95%) without any 1,4-reduction product detectable by GC. Adding acetic acid initially allows complete reduction overnight.

Sinapyl Alcohol 2b. *(E)*-Sinapaldehyde **1b** (130 mg, 0.62 mmol) was reduced as described for **1a** to yield crude *(E)*-sinapyl alcohol **2b** as a pale yellow syrup (120 mg, 91%). Again, no dihydrosinapyl alcohol could be detected by NMR or GC. For large scale preparation, sinapaldehyde **1b** (5.0 g, 24.0 mmol) was reduced overnight as described for **1a** to yield crude sinapyl alcohol **2b** as a pale yellow syrup (4.85 g, 96%). Crystallization of sinapyl alcohol is difficult (Quideau and Ralph, 1992). The product produced by using this method is suitable for use without further purification.

RESULTS AND DISCUSSION

Sodium borohydride is a versatile and relatively mild reducing agent generally used for the reduction of aldehydes and ketones. However, reduction of conjugated aldehydes and ketones with sodium borohydride is highly solvent dependent and generally does not result in useful regioselectivity (Nutaitis and Bernardo, 1989). It is not surprising that coniferyl alcohol prepared by sodium borohydride reduction of coniferaldehyde was contaminated with saturated coniferyl alcohol (Ludley and Ralph, 1996). Furthermore, we were unable to obtain the claimed selectivity using the procedure in that paper. GC showed that ~3% (not <1%) levels of dihydroconiferyl alcohol **3a** were obtained when coniferaldehyde was reduced by sodium borohydride in ethyl acetate (Figure 1).

Selective 1,2-reduction is usually achieved by the use of modified hydride reagents, which are formed by replacing hydride with bulky substituents or electron-withdrawing groups. For example, sodium (mono- and tri-)acetoxyborohydrides, prepared by adding controlled amounts of acetic acid to sodium borohydride in a solvent, reduced enones and enals in THF more selectively than the parent sodium borohydride (Nutaitis and Bernardo, 1989). $NaBH(OAc)_3$ reduced aldehydes in the presence of ketones (Gribble and Ferguson, 1975). $NaBH(OAc)_3$ was chosen for preparing coniferyl and sinapyl alcohols, even though it is weaker in reactivity than sodium monoacetoxyborohydride, because it is commercially available and more easily prepared in situ from $NaBH_4$ that is already stocked in most laboratories. Excess acetic acid does not replace the remaining hydride, but excessive amounts are avoided here to simplify the workup. Coniferaldehyde **1a** and sinapaldehyde **1b** were smoothly reduced to coniferyl alcohol **2a** and sinapyl alcohol **2b** by sodium triacetoxyborohydride, generated in situ, in ethyl acetate with no detectable 1,4-reduction product (Figure 1). The yields were 97 and 92% for **2a** and **2b**, respectively. The same selectivity was obtained with commercial $NaBH(OAc)_3$, although the reduction rate was slower in that case. Addition of acetic acid accelerated the reduction without impairing its selectivity. Coniferyl alcohol **2a** was crystallized from methylene chloride/petroleum ether in 70% yield. Multigram quantities of coniferyl alcohol and sinapyl alcohol were prepared in the same way without any difficulty, and coniferyl alcohol was easily crystallized in 77% yield. Attempts to crystallize sinapyl alcohol from methylene chloride/petroleum ether were unsuccessful; although it can be done (Quideau and Ralph, 1992), the low melting point makes crystallization capricious. We and others have had this difficulty in the past, and it is not indicative of less pure sinapyl alcohol. Crude sinapyl alcohol was pure enough to be used directly for making DHPs or other purposes.

The major advantages of this method are as follows: (1) the reducing agent, sodium triacetoxyborohydride, is either available from commercial sources or easily generated from sodium borohydride and can be used directly without requiring particular caution (users should adhere to safety precautions described, for example, in standard material safety datasheet information; hydrogen gas is liberated when HOAc is added to make the triacetoxyborohydride); (2) large scale preparations can be easily accomplished by using this method with similar results; and (3) the required products are prepared in high yields without any 1,4-reduction that produces the contaminant saturated alcohols that have always existed in previously described reductive methods.

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