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Simplified Preparation of Coniferyl and Sinapyl Alcohols

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Coniferyl and sinapyl alcohols were prepared from commercially available coniferaldehyde and sinapaldehyde using borohydride exchange resin in methanol. This reduction is highly regioselective and exceptionally simple, making these valuable monolignols readily available to researchers lacking synthetic chemistry expertise.

KEYWORDS: Coniferyl alcohol; sinapyl alcohol; coniferaldehyde; sinapaldehyde; lignin; borohydride exchange resin; Amberlite IRA-400

INTRODUCTION

The synthesis of high-quality monolignols, the 4-hydroxycinnamyl alcohols (coniferyl and sinapyl alcohols), has been an important step for successful preparation of lignans, synthetic lignin model compounds, and synthetic lignins or dehydrogenation polymers (DHPs). Many multistep synthetic methods have been developed to prepare such monolignols from various commercially available starting materials (*1*−*6*). Reductions of ferulate and sinapate with lithium aluminum hydride (*1*, *7*, *8*), sodium bis(2-methoxyethyl) aluminum hydride (Red-Al) (*9*, *10*), or diisobutyl aluminum hydride (DIBAL-H) (*11*) have all been used to prepare 4-hydroxycinnamyl alcohols.

Since 4-hydroxycinnamaldehydes (coniferaldehyde and sinapaldehyde) have become commercially available, several borohydride reagents have been used to prepare 4-hydroxycinnamyl alcohols by one-step reductions instead of the multistep syntheses previously used. Recently, the reduction of 4-hydroxycinnamaldehydes with sodium borohydride (*12*, *13*) and sodium triacetoxyborohydride (*14*−*16*) was examined (*17*, *18*). All of the described methods require handling moderately reactive and toxic reagents, and the quality of the product depends on nontrivial workup steps. Time-consuming reactions can also be a frustration.

Since Gibson and Baily first reported the preparation and use of borohydride exchange resin (BER) in 1977 (*19*), it has been used to reduce a variety of functional groups. Regioselective reduction of carbonyl compounds in alcoholic solvents is one of its most important uses (*20*, *21*). BER provides many of the practical advantages of other polymer-supported reagents in organic reactions (*22*, *23*). BER is more stable than sodium borohydride itself and easier to handle (*24*).

Coniferyl and sinapyl alcohols are commercially available now, but are 8−10 times more expensive than 4-hydroxycinnamaldehydes. Even when the expenses for resin and solvents are considered, the total cost of synthesizing the 4-hydroxycinnamyl alcohols is 2−3 times lower than for the commercial products. More importantly, the purchased products are sometimes of vastly inferior quality, often containing degradation products, particularly in the case of sinapyl alcohol. Obliviously using these compounds without carefully checking their purity first has caused problems for several researchers.

Here we report a simple protocol that produces clean coniferyl or sinapyl alcohol from coniferaldehyde or sinapaldehyde using BER. This method is efficient and can be safely performed without complication within short periods of time to produce fresh, clean 4-hydroxycinnamyl alcohols.

EXPERIMENTAL METHODS

General. NMR analyses of the coniferyl and sinapyl alcohols in acetone-d_6 were performed on a Bruker Avance-360 spectrometer. The central acetone solvent peak was used as the internal reference (^{1}H, 2.04 ppm; ^{13}C, 29.80 ppm). The NMR data were identical to those previously reported (*11*) and available in the lignin model compound database (*25*). Coniferaldehyde, sinapaldehyde, and "borohydride, polymer supported" [borohydride exchange resin, BER; 2.5−5.0 mmol of $BH^-{}_4$/g of resin; the borohydride ($BH^-{}_4$) concentration was assumed as 2.5 mmol/g of resin for calculations, even though the reagent had a designated concentration of 2.5−5.0 mmol of $BH^-{}_4$/g of resin] were purchased from Aldrich (Milwaukee, WI). All solvents were purchased from Fisher Scientific (Pittsburgh, PA) unless otherwise noted. Silica gel 60 (particle size = 0.040−0.063 mm, 230−400 mesh ASTM) was purchased from EMD Chemicals Inc. (Gibbstown, NJ). Solid-phase extraction (SPE) tubes (Supelclean, LC-SI, 3 mL) were purchased from Supelco (Bellefonte, PA). The 4-hydroxycinnamyl alcohol products were examined by GC-MS. GC (ThermoQuest Trace GC 2000) conditions were as follows: Zebron ZB-5 column (30 m × 0.25 mm, 25 μm film thickness, Phenomenex); initial column temperature, 220 °C, held for 1 min, ramped at a rate of 4 °C/min to 248 °C, then ramped at rate of 30 °C/min to 300 °C for 20 min; inlet temperature, 300 °C. MS (ThermoQuest GCQ/Polaris MS) conditions were as follows: ion

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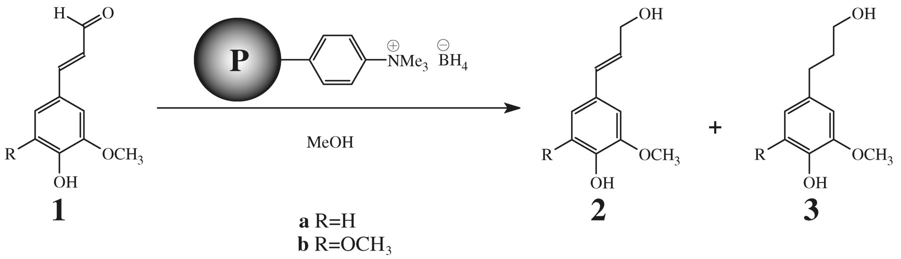

Figure 1. Reduction of coniferaldehyde **1a** and sinapaldehyde **1b** by borohydride exchange resin (BER).

source temperature, 225 °C; transfer line temperature, 325 °C; final temperature, 300 °C; positive-ion mode. Quantification of 1,4-reduction products **3**, low-level contaminants of desired products **2**, was via GC-MS using response factors derived from authentic compounds.

Synthesis of Coniferyl Alcohol 2a. BER (22.5 g, 56.1 mmol, 2 equiv) was introduced into a round-bottom flask (300 mL) and washed with methanol (150 mL × 3) before the reaction. Methanol was decanted from the resin each wash cycle. Fresh methanol (200 mL) was added to the flask, and then solid coniferaldehyde **1a** (5 g, 28.1 mmol, 1 equiv) was added directly to the mixture. The reaction mixture was stirred at room temperature for 1 h. The initial intense yellow color of the reaction solution faded to a pale yellow, and the color of the resin darkened during the reduction. The reaction may be monitored by TLC ($CHCl_3$/EtOAc, 1:1; $R_f = 0.32$). The resin was filtered through a plug of cotton wool in the stem of a funnel (or through a sintered glass filter) and washed with methanol (100 mL × 3). The filtrate was concentrated to a yellow oil with a rotary evaporator. Cleanup by passing through silica gel was accomplished as follows. Silica gel (11 g) was introduced into a 60 mL sintered glass filter funnel (medium porosity) and washed with ethyl acetate (50 mL × 3), discarding the eluant. The crude product was dissolved in ethyl acetate (30 mL), and the cloudy solution was transferred via pipet onto the silica gel surface. Without being allowed to dry, the product was eluted with ethyl acetate (50 mL × 3). The collected eluant was evaporated and spontaneously yielded a pale yellow crystalline mass (2.36 g, 13.1 mmol, 47%). NMR showed that the product contained only a trace of 1,4-reduction product **3a**, which was also detected at low levels (<0.03%) by GC-MS. Recrystallization may be carried out from dichloromethane/petroleum ether and afforded pale yellow needles: mp 73−75 °C [lit. (*11*) 77.9−78.6 °C; (*7*) 74−76 °C].

Small-scale preparation (coniferaldehyde **1a**, 205 mg, 1.15 mmol, 1 equiv; BER, 920 mg, 2.3 mmol, 2 equiv) was performed as for the large-scale synthesis. Silica gel cleanup in this case was most conveniently carried out using commercial 3 mL silica gel SPE tubes (first washing with 5 mL of ethyl acetate, then applying the crude product in 5 mL of ethyl acetate and eluting with 25 mL of ethyl acetate). A pale yellow crystalline mass (128 mg, 0.71 mmol, 62%) was obtained.

Synthesis of Sinapyl Alcohol 2b. Sinapaldehyde **1b** (5 g, 24 mmol, 1 equiv) was reduced by BER (19.2 g, 48 mmol, 2 equiv) in methanol, as described for coniferaldehyde **1a**. It was stirred for 3 h at room temperature to complete the reaction, and the reaction was monitored by TLC ($CHCl_3$/EtOAc, 1:1; $R_f = 0.29$). Following analogous filtering, sinapyl alcohol **2b** (3.64 g, 17.32 mmol, 72%) was obtained as a pale yellow oil. In this case, no 1,4-reduction product **3b** was observed in the ^{1}H NMR spectrum, but a trace (<0.05%) could be detected by GC-MS. The product was pure enough to use without further purification or crystallization. Crystallization of sinapyl alcohol **2b** is difficult (*11*) but possible. The pale yellow oil was dissolved in dichloromethane (5 mL) and kept in a freezer for several days. Pale yellow crystals formed.

Small-scale preparation (sinapaldehyde **1b**, 200 mg, 0.96 mmol, 1 equiv; BER, 770 mg, 1.92 mmol, 2 equiv) required stirring for 3 h to effect complete reduction, as shown by TLC monitoring, and yielded a pale yellow oil (147 mg, 0.70 mmol, 73%).

RESULTS AND DISCUSSION

Simple Procedure. Coniferyl alcohol **2a** and sinapyl alcohol **2b** were prepared from commercially available coniferaldehyde **1a** and sinapaldehyde **1b** using BER in methanol (**Figure 1**). The reactions needed to stir for an hour for coniferaldehyde **1a** and for 3 h for sinapaldehyde **1b** to complete the reduction. The reaction scaled proportionally; the procedures for large-scale and small-scale reactions were analogous. The resin changed color, from pale yellow to red-brown, and the yellow color of the reaction solution discharged when the reduction was complete. The reduction can be monitored easily by TLC ($CHCl_3$/EtOAc, 1:1). A particularly attractive aspect of this method is that conventional workup extractions are not required. Moderate yields are the only disadvantage—47% (61% for small-scale) for coniferyl alcohol **2a** and 72% (73% for small-scale) for sinapyl alcohol **2b**. Absorption of 4-hydroxycinnamyl alcohols into the coarse polymer resin and binding to phenolic groups by the quaternary ammonium group of the resin are among possible reasons, especially for the large-scale reaction of coniferyl alcohol. Changing the workup solvent to dichloromethane was not beneficial. Attempts to increase yields by adding acetic acid produced products contaminated with degraded products (which were revealed in NMR spectra, but the structures were not identified). The yield detriment is offset by the simplicity of the procedure. The products are extremely clean and ready to use without further purification. Coniferyl alcohol **2a** can be crystallized (*11*) and stored at room temperature for years. Sinapyl alcohol **2b** is difficult to crystallize and may degrade easily at room temperature. In our experience, sinapyl alcohol **2b** containing residual solvent is less likely to degrade. It must be kept in a freezer for long-term storage. Alternatively, adding 0.1% BHT (butylated hydroxytoluene; 3,5-di-*tert*-butyl-4-hydroxytoluene) in acetone to the product solution before drying may prevent oxidation and prolong its life. Even crystals should be stored in the freezer.

This protocol is a safe and efficient method, but there are two precautions that need to be taken to ensure success. First, the BER needs to be washed with methanol before use. This results in much less of the troublesome 1,4-reduction products (see below), presumably due to removal of unbound borohydrides. Washed resin can be stored for several days, but it is not recommended. Second, the crude products should be passed through prewashed silica gel to remove contaminants from the resin. This procedure is also beneficial to crystallize both 4-hydroxycinnamyl alcohols.

Advantages. BER has significant advantages over other reagents used to reduce 4-hydroxycinnamaldehydes in the past several years. Sodium borohydride in ethyl acetate produces coniferyl and sinapyl alcohols **2** from coniferaldehyde **1a** and sinapaldehyde **1b** (*17*); however, significant amounts of α,β-saturated products, dihydroconiferyl and dihydrosinapyl alcohols **3**, are also generated by 1,4-reduction due to the lack of regioselectivity and high solvent dependency (*15*, *17*, *18*). Modified weak hydride reagents, such as sodium triacetoxyborohydride, provide more selective 1,2-reduction for conjugated aldehydes, but the reaction time is long even when freshly prepared reagent is used (*16*, *18*).

BER exhibits a high regioselectivity between aldehydes and ketones, reducing aldehydes more quickly than ketones (*20*) and reducing α,β-unsaturated aldehydes without 1,4-reduction (*21*). Commercially available BER is strong enough to complete the required reduction within hours. The products from reduction of either of the 4-hydroxycinnamaldehydes were remarkably clean as evidenced by ^{1}H NMR spectra; the (un-recrystallized) coniferyl alcohol **2a** product contained ~0.03% dihydroconiferyl alcohol **3a,** and the sinapyl alcohol **2b** product contained ~0.05% dihydrosinapyl alcohol **3b**. There were essentially no differences between large-scale and small-scale preparations. Large-scale preparation does not require longer reaction times. Contaminants from the polymer-supported reagent can be readily removed from the desired products by simple "plug-filtration" through silica gel, and no extensive workup is needed. The products were ready to use without further purification or crystallization, but both 4-hydroxycinnamyl alcohols can be recrystallized to enhance their quality and shelf life.

The used resin can be recovered and recycled (*21*). Because the resin is relatively nontoxic and nonvolatile, it is easily handled by nonchemists.

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