A Convenient Synthesis of Coniferyl Alcohol

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Introduction

Lignin is a complicated natural aromatic polymer derived from enzyme-mediated dehydrogenation of 4-hydroxycinnamyl alcohols **a-c** (Fig. 1). So far a lot of effort has been expended to elucidate the lignin structure and its chemical relationships to cell wall components such as carbohydrates and phenolics. Because of their relative simplicity and their uniqueness 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. However, such investigations are usually difficult to carry out due to the poor accessibility of the 4-hydroxycinnamyl alcohols.

Several synthetic methods of 4-hydroxycinnamyl alcohols have been developed. However, all of them suffer from either low yield, undesirable contaminants, or difficult to handle reagents. Here we report a convenient synthesis of coniferyl alcohol **b** (Fig. 1), one of the most widely used 4-hydroxycinnamyl alcohols for DHPs.

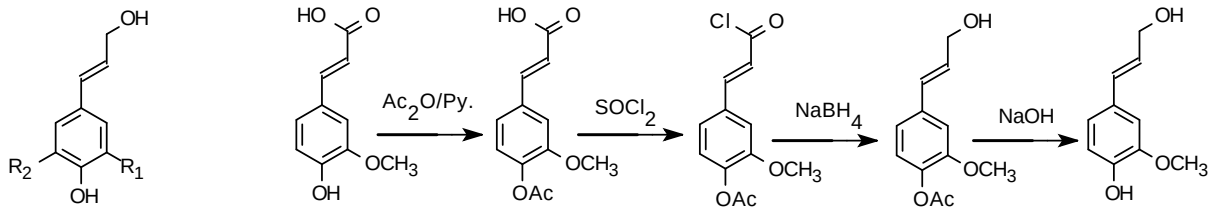
Methods

A) 4-Acetoxylferulic acid **2** is prepared from ferulic acid **1** by acetylation using Ac_2O/Pyridine and crystallized from ethanol after standard work-up, 96% yield.

B) 4-Acetylferuloyl chloride **3** is made as follows: compound **2** (5 g) is suspended in toluene (120 ml) with thionyl chloride (5 ml) at 80°C for 20 min, followed by addition of a catalytic amount of pyridine. In about 10 min, a clear solution is obtained accompanied by a settling out of an insoluble oil. The supernatant is transferred to a 500 ml flask and co-evaporated with toluene several times. A pure light yellow solid chloride is obtained in 96% yield and is used directly. It can be crystallized from hot toluene and stored for extended periods.

C) 4-Acetoxylconiferyl alcohol **4**: Compound **3** (1 mmole) is dissolved in ethyl acetate (10 ml distilled), followed by addition of sodium borohydride (4.5 eq). The mixture is stirred and monitored by TLC until the reaction is complete (1.5 h). After standard work-up, 4-acetoxyconiferyl alcohol is obtained in 95% yield.

D) Coniferyl alcohol **5:** To a solution of compound **4** (1 mmole) in ethanol (15 ml) is added NaOH (2 N, 2 ml) and this solution is stirred for 2 h at r.t. under N_2. The solution is acidified with 3% HCl and extracted with ethyl acetate. Normal work-up gives coniferyl alcohol (90%) as an oil which is crystallized from ethyl acetate/petroleum ether (pale yellow crystals, yield not calculated).



a $R_1 = R_2 = H$
b $R_1 = OCH_3$, $R_2 = H$
c $R_1 = R_2 = OCH_3$

1 **2** **3** **4** **5**

Figure 1. Preparation of hydroxycinnamyl alcohols from acid chlorides.

Discussion

It is well known that the selectivity of sodium borohydride reduction is highly solvent dependent, although most reductions using sodium borohydride are performed in alcoholic solvent systems. Acid chlorides have been reduced to alcohols by sodium borohydride in inert solvents such as dioxane. However, in the initial studies, α,β-unsaturated acid chlorides were reduced to saturated alcohols in low yield. Sodium borohydride adsorbed on alumina was shown to reduce acid chlorides to alcohols and α,β-unsaturated acid chlorides to allylic alcohols. Sodium borohydride has been used in THF for reductions of conjugated enones and enals with variable regioselectivities.

Monoacetoxyborohydride, generated in situ by addition of one equivalent of glacial acetic acid to a suspension of sodium borohydride in dry THF, has been reported to be capable of reducing conjugated enones and enals to allylic alcohols in good yields.

We recently found that sodium borohydride in ethyl acetate at room temperature is capable of converting α,β-unsaturated acid chlorides efficiently to primary allylic alcohols in high yields. Since 4-acetylferuloyl chloride can be prepared easily from 4-acetoxylferulic acid, and that sodium borohydride is a mild, cheap and easy to handle reducing agent, it would be an attractive and convenient way to synthesize coniferyl alcohol from ferulic acid by using sodium borohydride reduction of the acid chloride **3**. In the scheme, every step involved has a high yield and is easily carried out without special precautions. This approach can also be applied to synthesis of coumaryl and sinapyl alcohols with good yield.

Conclusion

We have developed a convenient and high yield method for synthesis of coniferyl alcohol from ferulic acid. A distinct advantage of the method is characterized by using sodium borohydride which is cheap and easily handled.