A New Synthesis of Coniferyl Aldehyde and Alcohol

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Abstract——Coniferyl aldehyde and alcohol, most important compounds as lignin monomers were synthesized by a new simple method. Methoxymethyl isoeugenol was oxidized with 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone (DDQ) to methoxymethyl coniferyl aldehyde, which gave coniferyl aldehyde by demethoxymethylation with AcOH. Reduction of the aldehyde with $NaBH_4$ gave coniferyl alcohol quantitatively.

Introduction

Coniferyl alcohol is one of the basic monomer units of lignin and has been used as a model compound and a precursor in lignin biosynthesis by many lignin chemists.

Coniferyl alcohol has been synthesized by reduction of ethyl ferulate with $LiAlH_4$ by the method of FREUDENBERG[1]. Recently, sodium dihydro-bis(2-methoxyethyl)alminate (RDB) was used instead of $LiAlH_4$ for reduction of the ethyl ferulate[2].

It is known, on the other hand, that the coloration of wood and lignin with phloroglucinol-HCl results from coniferyl aldehyde moiety in the lignin molecules. The aldehyde is known to be formed in the course of dehydropolymerization of coniferyl alcohol[3], and also to be the direct precursor of coniferyl alcohol in lignin biosynthesis[4].

Preparation methods of the aldehyde were reported[5] and the synthetic method was improved recently by the present authors[6].

In the present paper, the authors reported a convenient preparation method of coniferyl alcohol from commercially available isoeugenol through coniferyl aldehyde, which is prepared by oxidation of methyl group to aldehyde in the presence of water.

Experimental

Mps were not corrected. Plates coated with Merck Kieselgel 60 PF_{254} were used for analytical and preparative t.l.c. The following spectrometers were used for

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spectral analyses of the synthetic compounds; IR: JASCO model IR-S, NMR: R-22 HITACHI high resolution NMR spectrometer (90MHz) with TMS internal standard, MS: SHIMADZU-LKB 9000 gas chromatograph-mass spectrometer (70 eV), UV: HITACHI model 124 double beam spectrometer.

Methoxymethyl isoeugenol (*I*)—Isoeugenol (5.0 g, 30.5 mM) (a mixture of *trans* and *cis* forms 3:1) was dissolved in 10 ml of DMF (dried with molecular seives) in a flask fitted with a magnetic stirrer and two addition funnels, and the reaction mixture was cooled to 0°C with ice bath. Sodium hydride (2.2 g, 45.7 mM) which was previously washed with dry petroleum ether, and suspended in dry DMF (30 ml) was added slowly into the reaction mixture and the temperature was kept at 0°C. After hydrogen evolution ceased, chloromethyl methyl ether (3.7 g, 45.7 mM) was introduced to the flask for 15 min. and the mixture was stirred for 2 hours in the cold. Wet ether (50 ml) and then water (50 ml) were added carefully to decompose the remaining sodium hydride. The resulting solution was poured into 50 ml of water, and the aqueous phase was extracted with ether (30 ml×4). The combined ether fractions were washed with 5% NaOH solution (30 ml×2) and saturated NaCl aq. successively, and dried over anhydrous Na_2SO_4. Evaporation of the solvents gave 5.7 g (90 %) of crude I as a pale yellow oil which could be used for further reaction without purification. I (5.3 g) was isolated by distillation as a colorless oil. Bp. 110°C/1.0 mmHg, (*trans* and *cis* mixture). R_f 0.35 (*n*-hexane-$CHCl_3$ 1:1). The spot was negative coloration for the spray of "Fast blue salt B" (diazonium reagent, Merck); NMR (CCl_4) δ (ppm): 1.8~1.9 (=C—CH_3), 3.41 (C—OCH_3), 3.75 (Ar—OCH_3), 5.03 (Ar—OCH_2O—), 5.50~6.34 (olefinic), 6.65~7.00 (Ar). MS *m/e* (relative intensity): 208 (63, M^+), 178 (59), 163 (28), 107 (12), 91 (11), 45 (100), m* (metastable peak): 152.33 (208→178), 149.26 (178→163).

Methoxymethyl coniferyl aldehyde (*II*)—To a solution of DDQ (13.1 g, 57.7 mM) in 500 ml of water-saturated benzene, was added a solution of I (5.0 g, 24.0 mM) in 100 m of benzene for 2 hours at room temperature. After 24 hours, a solution of ascorbic acid (10.2 g, 57.7 mM) in 150 ml of water was added to the reaction mixture to reduce the excess DDQ to the corresponding hydroquinone (DDHQ). The DDHQ was filtered off (12.7 g), washed with benzene (50 ml×3) and then water (50 ml×2). The combined filtrates were transfered to a separating funnel and the organic phase was washed with saturated NaCl aq. and dried over anhydrous Na_2SO_4, and the solvent was removed by evaporation under a reduced pressure. The product (6.2 g) was chromatographed on a silica gel column (3×50 cm), and eluted with ethyl acetate-benzene (1:9). Each eluate was checked with phloroglucinol-HCl test and the fractions containing the product were evaporated to dryness. A crude product of II was recrystallized from benzene (3.8 g, 72%). Mp. 77~

77.5°C (lit.[5] 77~78°C), colorless needles. R_f 0.43 (ethyl acetate-benzene 1:9), pink coloration with phloroglucinol-HCl. IR (KBr) ν (cm^{-1}): 2830, 2790, 1677 (—CHO), 1598, 1514, 1277, 1263, 1160, 1138, 990 (*trans* C=C), 800. NMR (CD_3COCD_3) δ (ppm): 3.46 (3 H, s, C—OCH_3), 3.91 (3 H, s, Ar—OCH_3), 5.23 (2 H, s, Ar—OCH_2O—), 6.66 (1 H, dd, J_1=15.5 Hz, J_2=7.5 Hz, =CH—CO), 7.16~7.37 (3 H, m, Ar), 7.55 (1 H, d, J_1=15.5 Hz, Ar—CH=), 9.67 (1 H, d, J_2=7.5 Hz, —CHO. MS *m/e* (rel. int.): 222 (64, M^+), 192 (16), 191 (6), 177 (8), 176 (6), 161 (12), 118 (4), 103 (4), 91 (5), 89 (4), 78 (5), 51 (6), 45 (100), m*: 166.05 (222→192).

Coniferyl aldehyde (III)—Methoxymethyl coniferyl aldehyde II (3.0 g, 13.5 mM) was dissolved in 15 ml of AcOH, containing 5 drops of *N* H_2SO_4, and the reaction mixture was stirred at room temperature for 15 hours. The mixture, which gave one spot on a t.l.c. plate, was poured on water (100 ml) and neutralized with dil. NaOH solution. The aqueous layer was extracted with $CHCl_3$ (30 ml×4), and the combined $CHCl_3$ was washed with saturated NaCl aq. and dried over anhydrous Na_2SO_4. The solvent was evaporated to dryness *in vacuo*. An oily product which immediately crystallized was obtained. It was recrystallized from hot benzene (2.28 g, 95%). The mother liquor was chromatographed on preparative t.l.c. (1% methanol $CHCl_3$) and 70 mg of III was recovered. Mp. 80~82°C (lit.[5] 82.5°C). R_f 0.44 (2% methanol $CHCl_3$), red purple coloration with phloroglucinol-HCl. IR (KBr) ν (cm^{-1}): 2850, 1683 (—CHO), 1600, 1520, 1435, 1295, 1140, 1120, 1028, 967 (*trans* C=C), 883, 813. NMR ($CDCl_3$) δ (ppm): 3.92 (3 H, s, Ar—OCH_3), 6.56 (1 H, dd, J_1=16.0 Hz, J_2=7.8 Hz, =CH—CO), 6.88~7.16 (3 H, m, Ar), 7.38 (1 H, d, J_1=16.0 Hz, Ar—CH=), 9,62 (1 H, d, J_2=7.8 Hz, —CHO). MS *m/e* (rel. int.): 178 (100, M^+), 177 (19), 163 (8), 147 (25), 135 (28), 119 (10), m*: 176.01 (178→177), 122.08 (177→147), 96.33 (147→119). UV (EtOH, max) λ (mμ) (ε): 340 (23,800).

Coniferyl alcohol (IV)—To a solution of $NaBH_4$ (18.8 g, 44.8 mM) in methanol (100 ml) was added dropwise at −5°C coniferyl aldehyde III (2.0 g, 11.2 mM) in 50 ml of methanol, and the solution was stirred for 12 hours at room temperature. The solution containing only coniferyl alcohol as a reaction product (checked by t.l.c.) was poured on water (150 ml) and neutralized with dil. HCl solution. The major portion of methanol was removed at 35°C and the aqueous layer was extracted with $CHCl_3$ (30 ml×4), and the combined $CHCl_3$ was washed with saturated NaCl aq. and dried over anhydrous Na_2SO_4. The solvent was removed by evaporation under a reduced pressure. A colorless oil which gradually crystallized was obtained. It was dissolved in ether and recrystallization was completed by the addition of petroleum ether (bp. 30~50°C) (1.88 g, 93%). Further 83 mg of IV was obtained from the mother liquor by preparative t.l.c. (3% methanol $CHCl_3$). Mp. 74~75°C

(lit.[1] 74~76°C), R_f 0.22 (2% methanol $CHCl_3$). IR (KBr) ν (cm^{-1}): 3570, 3300, 1603, 1526, 1269, 1230, 1085, 1010, 958 (*trans* C=C), 851. NMR ($CDCl_3$) δ (ppm): 3.86 (3 H, s, Ar—OCH_3), 4.27 (2 H, d, J_2=5.5 Hz, —CH_2OH), 6.17 (1 H, dt, J_1= 15.8 Hz, J_2=5.5 Hz, =CH—C), 6.52 (1 H, d, J_1=15.8 Hz, Ar—CH=), 6.83 (3 H, m, Ar). MS *m/e* (rel. int.): 180 (81, M^+), 167 (17), 162 (44), 152 (10), 149 (9), 147 (30), 138 (13), 137 (100), 131 (23), 124 (41), 119 (34), 109 (10), 103 (16), 91 (39), 77 (16), 65 (16), m*: 104.27 (180→137), 69.59 (119→91). UV (EtOH, max) λ (mμ) (ε): 265 (17,400), 301 (9,800).

Recovery of DDQ—Crude DDHQ obtained from the reaction mixture of the preparation of III was oxidized to DDQ by the method of WALKER and WAUGH[7]. Powder of DDHQ (5.0 g) was suspended in a mixture of water (35 ml) and a conc. HCl (35 ml). A conc. nitric acid (10 g, 69 %) was added to the mixture for 45 min. at room temperature. The solution was warmed to 40°C with stirring for 1 hour, and poured into 200ml of water. The aqueous phase was extracted with benzene (50 ml×6). The combined organic phase was washed with saturated NaCl aq. and dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvents gave 3.0 g (61%) of DDQ as red crystals. Pure DDQ (2.4 g) was obtained by recrystallization with benzene and petroleum ether (bp. 30-50°C) and it was yellow needles when dried. Mp. 210°C (lit.[7] 212-213°C).

Results and Discussion

It was reported that oxidation of β-methylstyrene and allylbenzene with DDQ in benzene yielded *trans*-cinnamaldehyde[8]. *trans*-Anethole was also found to be oxidized to 4-methoxy-*trans*-cinnamaldehyde with this reagent[9].

When isoeugenol was preliminarily treated with DDQ (three molar quantity) in water-saturated benzene at room temperature, a trace amount (2%) of coniferyl aldehyde was obtained. The lower yield of the product in the reaction was found to result from the oxidative polymerization of isoeugenol.

Therefore, *trans*-acetyl isoeugenol (separated from *cis* isomer as crystals) was subjected to the DDQ oxidation, but the reaction did not proceed even if in the presence of excess DDQ and refluxing of the reaction mixture. It was reported[8] that 4-methoxy-β-methylstyrene was at least 100 times more reactive than β-methylstyrene with DDQ. The fact may indicate that the electron-attracting groups such as acetoxyl at *p*-position of side chain inhibited the hydride shift from terminal group to DDQ. The result together with the previous observations suggest that the electron-releasing groups at *p*-position of side chain, such as methoxyl, methoxymethoxyl and *O*-tetrahydropyranyl, were preferable as the protecting groups of phenol. Then in the present experiment, isoeugenol was protected with chloromethy methyl ether

to form acetal bond. As this derivative was stable under neutral and alkaline conditions but in acidic one, good results were obtained in the subsequent reactions.

Commercially available isoeugenol was a mixture of *trans* and *cis* isomers (about 3 : 1), and methoxymethyl isoeugenol also contained both isomers after distillation. However, the oxidation of this mixture with DDQ gave only methoxymethyl-*trans*-coniferyl aldehyde as crystals (72 % yield). This result was expected to be reasonable, since it was reported[8] that *trans*-β-methylstyrene yielded *trans*-cinnamaldehyde in good yield (55 %) but *cis* isomer gave *trans*-cinnamaldehyde in lower yield (27 %), respectively.

DDQ is an expensive reagent but it could be easily recovered by the method of WALKER and WAUGH[7] (see Experimental).

Coniferyl aldehyde was obtained as pure crystals by deprotection of the methoxymethyl derivative with AcOH. Furthermore, reduction of the aldehyde to the corresponding alcohol with $NaBH_4$ proceeded quantitatively, and pure crystals of coniferyl alcohol were obtained without further purification. Coniferyl alcohol is relatively unstable to light, oxygen, moisture and high temperature, and it is preferable to isolate pure compound as possible. In view of these facts, this synthetic method is very effective to obtain the desired alcohol as pure crystals.

In a similar manner as described in the experimental section, methoxymethyl coniferyl aldehyde was reduced with $NaBH_4$ and the corresponding alcohol was obtained quantitatively. But the deprotection of methoxymethyl coniferyl alcohol to coniferyl alcohol with AcOH was unsuccessful, because the alcohol was not stable under these conditions.

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