Regiospecific conversion of substituted cinnamic acids to cinnamyl alcohols

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A selective reduction of cinnamic acids with oxygen functionalities in aromatic ring to the corresponding alcohols with retention of double bond using ClCO_2Et , $\text{Et}_3\text{N}/\text{NaBH}_4$ is reported.

In continuing our study¹ on lignan synthesis we needed to prepare a variety of cinnamyl alcohols having oxygen functionalities at the aromatic ring. Several methods²⁻⁷ are available for the reduction of carboxylic acids to primary alcohols. But, out of these methods only very few reports are there for the conversion of cinnamic acid to cinnamyl alcohol. For example, *N,N*-dimethylchloromethyl-eniminium chloride/ NaBH_4 ³, NaBH_4/I_2 ⁴, imidazolid/ NaBH_4 ⁵, DCC/LiBH_4 ⁶ and BOP reagent/ NaBH_4 ⁷ have been utilized to reduce only cinnamic acid to cinnamyl alcohol⁸. Although a large number of biologically active aromatic naturally occurring compounds⁹ contain oxygen functionalities at their aromatic ring, there is no report so far on the conversion of cinnamic acids having oxygenated functionalities at the aromatic ring to the corresponding cinnamyl alcohols. These alcohols may be exploited as building blocks for the synthesis of various natural products¹⁰. To satisfy our requirement of substituted cinnamyl alcohols in lignan synthesis, we have converted a number of cinnamic acids with oxygen functionalities to the corresponding cinnamyl alcohols using ClCO_2Et , $\text{Et}_3\text{N}/\text{NaBH}_4$ ¹¹ (Scheme 1). The reaction takes place regiospecifically on carboxylic group without affecting the double bond. To the best of our knowledge, this is the first report of the reduction of substituted cinnamic acid to cinnamyl alcohols,

which would make valuable contributions to synthetic organic chemistry. A variety of mono and disubstituted cinnamyl alcohols have been synthesized by this method in good to excellent yields (Table 1).

Experimental

The IR spectra were run on Perkin-Elmer 782 spectrophotometer. ¹H NMR spectra were determined in *d*-chloroform solution on Bruker AM300L instrument operating at 300 MHz and reported in δ ppm using TMS as the internal standard.

General procedure :

Cinnamic acid (3.52 mmol) was dissolved/suspended in dry THF (5 ml) and cooled to -15° . Dry Et_3N ¹² (387.8 mg, 3.84 mmol) in dry THF (2 ml) and ClCO_2Et ¹² (416.6 mg, 3.84 mmol) in dry THF (2 ml) were injected slowly and separately at a time during 2 h into the stirred solution at -15° . The reaction mixture was warmed to 0° during 1 h and left stirring at 0° for a further period of 2 h. The resultant precipitate was filtered off and NaBH_4 (0.28 g, 7.4 mmol) was added to the filtrate and stirred. The reaction mixture was then quenched with 10% hydrochloric acid at 0° . The product was extracted with ether (3×10 ml) and washed with brine and dried over anhydrous sodium sulphate. Evaporation of the solvent followed by the filtration on a short silica gel column afforded the pure desired products.

The IR and ¹H NMR spectral data of the products (entry 1-7) are given below : *Entry 1* : ν_{max} (neat) 3350 (br), 3020, 2920, 1650, 1590, 1490, 960, 730 cm^{-1} ; ¹H NMR δ 7.24-7.08 (5H, m, Ar-H), 6.45 (1H, d, *J* 15.9 Hz, 3-H), 6.20 (1H, m, 2-H), 4.14 (2H, dd, *J* 5.6, 1.2 Hz, CH_2OH), 3.20 (1H, br s, OH); ¹³C NMR δ 134.0 (C-3), 128.5 (C-3'), 127.7 (C-4'), 126.5 (C-2'), 123.2 (C-2), 64.6 (CH_2OH) ppm; *Entry 2* : ν_{max} (neat) 3400 (br), 3000, 1770, 1610, 1600, 1450, 1400, 1020, 800 cm^{-1} ; ¹H NMR δ 7.28 (2H, d, *J* 8.5 Hz, 2'-H, 6'-H), 7.03 (2H, d, *J* 8.5 Hz, 3'-H, 5'-H), 6.49 (1H, d, *J* 15.9 Hz, 3-H), 6.21 (1H, m, 2-H), 4.23 (4H, m, CH_2OH , OCH_2CH_3), 3.54 (1H, br s, OH), 1.53 (3H, t, *J* 7.1 Hz, OCH_2CH_3) ppm; *Entry 3* : ν_{max} (neat) 3400-3000 (br), 2960, 1770, 1600, 1450, 1400, 940, 710 cm^{-1} ; ¹H NMR δ

Table 1. Results of reduction of substituted cinnamic acids to cinnamyl alcohols

Entry no.	Substrate	Product	Temp ^{a,b} °C	Time ^a h	yield ^c %
1			0–5	2.5	96
2			0–2	3.0	80
3			0–2	3.0	88
4			0–2	3.0	76
5			0	3.0	89
6			0–2	5.0	80
7			0	3.0	96

^aFor NaBH₄ addition. ^bIncrease in temperature led to saturated alcohols. ^cYields based on isolation of chromatographically homogeneous products.

7.30–7.05 (3H, m, Ar-H), 6.98 (1H, dd, *J* 7.1, 1.1 Hz, 5'-H), 6.51 (1H, d, *J* 15.9 Hz, 3-H), 6.27 (1H, d, *J* 15.9 Hz, 2-H), 4.23 (4H, m, CH₂OH, OCH₂CH₃), 1.30 (3H, t, *J* 7.1 Hz, OCH₂CH₃) ppm; **Entry 4**: $\nu_{\max}$ (KBr) 3400 (br), 3000, 1660, 1620, 1450, 1400, 940, 810 cm⁻¹; ¹H NMR δ 7.22 (2H, d, *J* 8.6 Hz, 2'-H, 6'-H), 6.76 (2H, d, *J* 8.6 Hz, 3'-H, 5'-H), 6.45 (1H, d, *J* 15.8 Hz, 3-H), 6.13 (1H, m, 2-H), 4.20 (2H, d, *J* 5.6 Hz, CH₂OH), 3.77 (3H, s, OCH₃) ppm; **Entry 5**: $\nu_{\max}$ (neat) 3400 (br), 3000, 1770, 1620, 1530, 1480, 1430, 1050, 820 cm⁻¹; ¹H NMR δ 7.26–6.52 (3H, m, Ar-H), 6.57 (1H, d, *J* 15.9 Hz, 3-H), 6.31 (1H, m, 2-H), 4.29 (4H, m, CH₂OH, OCH₂CH₃), 3.83 (3H, s, OCH₃), 2.04 (1H, s, OH), 1.38 (3H, t, OCH₂CH₃); ¹³C NMR δ 153.2 (C=O), 151.0 (C-3), 139.4 (C-4), 135.9 (C-1'), 130.0 (C-3), 129.0 (C-6'), 122.7 (C-2), 118.9 (C-5'), 110.1 (C-2'), 64.8 (CH₂OH), 63.2 (OCH₂CH₃), 55.7 (OCH₃), 14.1 (OCH₂CH₃) ppm; **Entry 6**: $\nu_{\max}$ (KBr) 3400 (br), 2960, 1670, 1600, 1510, 1450, 970, 800 cm⁻¹; ¹H NMR δ 6.85 (1H, d, *J* 1.5 Hz, 2'-H), 6.74 (1H, dd, *J* 8.0, 1.5 Hz, 6'-H), 6.67 (1H, d, *J* 8.0 Hz, 5'-H), 6.44 (1H, d, *J* 16.4 Hz, 3-H), 6.11 (1H, m, 2-H), 5.87 (2H, s, OCH₂O), 4.21 (2H, m, CH₂OH), 1.69 (1H, br s, OH) ppm; **Entry 7**: $\nu_{\max}$ (KBr) 3400 (br), 3020, 2960, 1610, 1590, 1470, 1400, 980, 810

cm⁻¹; ¹H NMR δ 6.94–6.77 (3H, m, Ar-H), 6.51 (1H, d, *J* 15.8 Hz, 3-H), 6.26 (1H, m, 2-H), 4.29 (2H, dd, *J* 5.8, 1.0 Hz, CH₂OH), 3.88 (6H, s, 2 × OCH₃); ¹³C NMR δ 149.3 (C-3', C-4'), 131.1 (C-3), 130.1 (C-1'), 126.6 (C-2), 119.7 (C-6'), 111.3 (C-2'), 109.8 (C-5'), 63.7 (CH₂OH), 56.0 (OCH₃) ppm.

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References

1. J. Mitra and A. K. Mitra, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1285; *Indian J. Chem., Sect. B*, 1992, **31**, 452; 1994, **33**, 953.
2. R. C. Larock, "Comprehensive Organic Transformations", VCH, New York, 1989; K. Soai, S. Yokoyama and K. Mochida, *Synthesis*, 1987, 647; A. Giannis and K. Sandhoff, *Angew. Chem. Int. Ed. Engl.*, 1989, **28**, 218; J. Das and S. Chandrasekaran, *Synth. Commun.*, 1990, **20**, 911; Y. Suseela and M. Periasamy, *Tetrahedron*, 1992, **48**, 371.
3. T. Fujisawa, T. Mori and T. Sato, *Chem. Lett.*, 1983, 835.
4. J. V. Kanath and M. Periasamy, *J. Org. Chem.*, 1991, **56**, 5964.
5. R. Sharma, G. H. Voynov, T. V. Ovaska and V. E. Marquez, *Synlett*, 1995, 839.

Note

6. J. M. Herbert, A. T. Hewson and J. E. Peace, *Synth. Commun.*, 1998, **28**, 823.
7. R. P. McGeary, *Tetrahedron Lett.*, 1998, **39**, 3319.
8. Refs. 5 and 7 reported that the same amount of saturated alcohol was also produced.
9. W. D. MacRae and G. H. N. Towers, *Phytochemistry*, 1984, **23**, 1207.
10. S. Hanessian and R. Leger, *Synlett*, 1992, 402.
11. ClCO_2Et , $\text{Et}_3\text{N}/\text{NaBH}_4$ have been used earlier to reduce cinnamic acid having no substitution to cinnamyl alcohol (K. Ishizumi, K. Koga and S. Yamada, *Chem. Pharm. Bull.*, 1968, **16**, 492). On utilising their reaction condition, we got an appreciable amount of saturated alcohol from cinnamic acid.
12. For entries **2**, **3** and **5**, 7.68 mmol of Et_3N and ClCO_2Et were used and phenolic-OH group has been converted to carbonate derivative.