A Facile, Rapid Preparation of a Series of Cinnamyl Alcohols from 3-Phenylpropenes Using Selenium Dioxide

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A number of methoxy- and methylenedioxy phenyl-1-(or -2-)-propenes occur in plants and are especially notable as constituents of the numerous spices and herbs used worldwide in human comestibles. Although some of these may well be harmless as ordinarily used in small amounts, a few have been found to be toxic and/or weakly hepatocarcinogenic, for example, safrole [3-(3,4-methylenedioxyphenyl)-propene], estragole [3-(4-methoxyphenyl)-propene], and β-asarone [*cis*-(2,4,5-trimethoxyphenyl)-2-propene]. The metabolism of the first two compounds has been studied extensively[1,2,3]. The 3-aryl-2-propenols (cinnamyl alcohols) are among the known or possible liver metabolites in the mouse or rat. In at least one case (4-methoxyphenyl), the 3-(4-methoxyphenyl)-2-propenol derivative is among the most toxic of its possible metabolites[4].

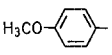
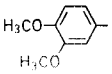
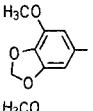
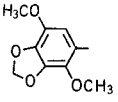
In the series of naturally occurring compounds under consideration, few of these cinnamyl alcohols are commercially available. Synthetic routes, with two steps required, have commonly started (a) with the cinnamic acid which is esterified with ethanol and reduced with lithium aluminum hydride or (b) with the corresponding benzaldehyde which with two equivalents of vinylmagnesium bromide yields the 3-aryl-1-propenol derivative. The latter, with mineral acid treatment, is rearranged to the desired cinnamyl alcohol. Overall yields in the range of 25–35% have been reported in a number of cases. For most of the compounds in this group, however, the 3-arylpropene derivative is readily available. Indeed, in some cases, it is the only commercially available form, e.g., apiol [3-(2,5-dimethoxy-3,4-methylenedioxyphenyl)-propene] and myristicin [3-(3-methoxy-4,5-methylenedioxyphenyl)-propene]. A rapid one-step process (substituted 3-arylpropene to the corresponding cinnamyl alcohol) is clearly desirable.

$$\underset{\mathbf{1}}{Ar{-}CH_2{-}CH{=}CH_2} + SeO_2 \xrightarrow{\text{dioxan / water}} \underset{\mathbf{2}}{Ar{-}CH{=}CH{-}CH_2{-}OH}$$

There is one example in the literature of oxidation of a 3-(methoxyphenyl)-propene by selenium dioxide[5]. Estragole was refluxed in acetic anhydride with selenium dioxide for five hours leading to a 27% yield of *p*-methoxycinnamyl acetate. We decided to modify this reaction using milder conditions with avoidance of ester formation. In general, a five-minute reaction at ~85 °C in dioxan (plus 10% water) with one equivalent of selenium dioxide led to 24–33% yields of the cinnamyl alcohols. This not only compares favorably with the overall yield reported from the two-step reactions cited above, but also involves easier purification.

3-Phenyl-1-propene itself was included for comparison. In this case a longer reaction time, together with the addition of hydrogen peroxide, improved the yield substantially, but these conditions were not effective for the other compounds.

Table. Oxidation of 3-Arylpropenes **1** to Cinnamyl Alcohols **2** (5 min at 85 ± 3 °C)

Product	Ar	Yield [%]	m.p. [°C] found	m.p. [°C] reported	Molecular formula[a]	I.R. (nujol) ν [cm⁻¹]	¹H-N.M.R. (CDCl₃/TMS/80 MHz) δ [ppm]
2a[b]		44	29–31°	33–34°[6]	—	identical with data in Ref.[6]	
2b		27	oil	b.p. 95–100°/ 0.4 torr[7]	$C_{10}H_{12}O_2$ (164.2)	3340, 1645, 1595, 1485, 1240, 1025, 970[c]	7.5–6.3 (m, 4 H_{arom}, H-1′, H-2′); 4.4–4.2 (m, 2H, H-3′); 3.84 (s, 3H, OCH_3); 1.58 (s, 1H, OH)
2c		30	77–78°	79°[4]	$C_{10}H_{12}O_2$ (164.2)	identical with data in Ref.[4]	
2d		25	76–79°	78°[8]	$C_{11}H_{14}O_3$ (194.2)	3520, 1600, 1560, 1510, 1260, 1220, 1150, 1135, 1080, 1020, 955, 910, 860, 770, 750	7.25 (s, 1 H_{arom}); 7.0–6.2 (m, 2 H_{arom}, H-1′, H-2′); 4.3–4.2 (m, 2H, H-3′); 3.88 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 1.59 (s, 1H, OH)
2e		33	77–78°	77°[9]	$C_{10}H_{10}O_3$ (178.2)	—	identical with data in Ref.[9]
2f		24	81–82°	—	$C_{11}H_{12}O_4$ (208.2)	3290, 3200, 1630, 1510, 1318, 1235, 1195, 1135, 1085, 1050, 962, 952, 925, 840, 815, 765	7.26 (s, 1 H_{arom}); 6.6–6.3 (m, 1 H_{arom}, H-1′, H-2′); 5.95 (s, 2H, OCH_2O); 4.3 (m, 2H, H-3′); 3.90 (s, 3H, OCH_3); 1.57 (s, 1H, OH)
2g		24	82.5–84.5	—	$C_{12}H_{14}O_5$ (238.2)	3220, 1630, 1600, 1500, 1345, 1230, 1180, 1135, 1060, 988, 960, 790	7.26 (s, 1 H_{arom}); 6.7–6.1 (m, 2H, H-1′, H-2′); 5.97 (s, 2H, OCH_2O); 4.4–4.2 (m, 2H, H-3′); 3.89 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 1.56 (s, 1H, OH)

[a] The microanalyses were in satisfactory agreement with the calculated values (C ±0.35, H ±0.18, O ±0.30), analyses performed by Huffman Laboratories.

[b] 30% Hydrogen peroxide (6 ml) is added in small portions keeping the temperature at 85 °C ± 3 °C, with a total reaction time of 47 min (see text).

[c] Neat oil.

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Cinnamyl Alcohols 2; General Procedure:

Powdered selenium dioxide (5.33 g, 0.048 mol) is dissolved in water (4 ml) by warming. To the stirred warm solution, dioxan (40 ml) and the 3-arylpropene **1** (0.046 mol) are added all at once. The mixture is then quickly heated with rapid stirring to ~85 °C for 5 min and cooled. It is then filtered, diluted with water (75 ml), and extracted with dichloromethane (3 × 25 ml). The extract is washed first with 10% aqueous sodium hydrogen carbonate (3 × 10 ml), then with brine (2 × 10 ml), and dried with anhydrous magnesium sulfate. Evaporation on a rotary evaporator at 35–40 °C (water aspirator) gives a crude material which is purified by dry column chromatography as follows.

Silica gel for dry column chromatography (ICN Nutritional Biochemical Catalog No. 404526, Brockmann Activity III/30 mm; 300–400 g) is equilibrated with ether/hexane (3:1, v/v; 30–40 g) and then tightly packed into a nylon tubing (25–32 mm diameter). The crude product, dissolved in ether (10–25 ml), is mixed with solvent-equilibrated silica gel (15–25 g) and the solvent is removed under reduced pressure. The dry mixture is then packed on top of the column and is covered with a layer of 8–12 mesh boiling stones. The column is then developed with ether/hexane (3:1, v/v). The product-band is removed and extracted with ether which is dried over molecular sieves, Linde 4A. The ether is then evaporated giving the product.

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