

## A Practical Synthesis of Olivetol

Ramesh Chander ANAND\* and Harish RANJAN

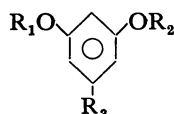
Department of Chemistry, Indian Institute of Technology, Hauz Khas, New Delhi-110 016, India

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**Synopsis.** A simple and practical synthesis of olivetol has been described in 55% overall yield from  $\alpha$ -resorcylic acid.

Recently there have been large interests in psychotomimetically active compounds of marijuana (hashish) because of their extensive biological activity.<sup>1)</sup> This has stimulated a number of synthetic efforts towards cannabinoids.<sup>2)</sup> The syntheses of these compounds depend largely on the availability of the key intermediate olivetol (5-pentyl-1,3-benzenediol) (1). This compound was first obtained by degrading lichen acid and olivetonic acid<sup>3)</sup> but later a number of synthetic routes have been developed.<sup>4)</sup> Most of the syntheses reported involve unsatisfactory overall yields, and/or the intermediates reported are predominantly liquids, the purification of which are relatively cumbersome. Moreover, the syntheses recorded are through the protection of two hydroxyl groups as their methyl ethers, the conversion of which into olivetol requires high temperature and this results in inferior quality product.

In the present communication, we wish to report a simple, efficient and practical synthesis of olivetol starting from commercially available  $\alpha$ -resorcylic acid (3,5-dihydroxybenzoic acid) (2). The intermediates isolated are solid, crystalline compounds and the deprotection of two benzyloxy groups at the end is carried out under mild reaction conditions. The synthesis of the title compound is as follows:



- 1  $R_1, R_2 = H; R_3 = n-C_5H_{11}$
- 2  $R_1, R_2 = H; R_3 = COOH$
- 3  $R_1, R_2 = CH_2C_6H_5; R_3 = COOCH_2C_6H_5$
- 4  $R_1, R_2 = CH_2C_6H_5; R_3 = CH_2OH$
- 5  $R_1, R_2 = CH_2C_6H_5; R_3 = CHO$
- 6  $R_1, R_2 = CH_2C_6H_5; R_3 = CH(OH)C_4H_9(n-)$

$\alpha$ -Resorcylic acid (2) was benzylated with potassium carbonate and benzyl chloride in DMF to give benzyl 3,5-bis(benzyloxy)benzoate (3) in 97% yield. Lithium aluminium hydride reduction of the benzyl ester followed by oxidation of the resulting alcohol (4) with pyridinium chlorochromate<sup>5)</sup> afforded 3,5-bis(benzyloxy)benzaldehyde (5). Grignard reaction of butylmagnesium bromide on the aldehyde (5) furnished the alcohol (6). Refluxing of 6 with *p*-toluenesulfonic acid in benzene under Dean and Stark apparatus followed by hydrogenation of the resulting product with 10% Pd/C at room temperature afforded olivetol in 55% overall yield.

## Experimental

Benzyl 3,5-Bis(benzyloxy)benzoate (3). This compound

was prepared by refluxing and stirring a mixture of  $\alpha$ -resorcylic acid (20 g; 0.129 mol), DMF (150 ml),  $K_2CO_3$  (107.64 g, 0.78 mol), and benzyl chloride (98.28 g, 0.78 mol). Reaction was monitored by TLC, after completion of the reaction (12 h), it was diluted with cold water and extracted with ether. Evaporation of solvent and crystallization of the residue with benzene-hexane afforded benzyl-bis(benzyloxy)benzoate (54.2 g, 97%), mp 63–66 °C,  $\nu_{max}$  3090, 3060, 3035, 2925, 1740, 1600, 1490, 1450, 1375, 1350, 1300, 1260, 1225, 1170, 1110, 1060–1030, 985, 945, 920, 875, 855–835, 760  $cm^{-1}$ . NMR:  $\delta$  4.88 (s, 4H), 5.24 (s, 2H), 6.64–7.2 (m, 18H).

3,5-Bis(benzyloxy)benzyl Alcohol (4). Benzyl ester (3, 54.0 g, 0.12 mol) was reduced with lithium aluminium hydride (9.12 g, 2 mol) in dry ether. It was decomposed with 5% hydrochloric acid. Removal of the solvent followed by crystallization from benzene-hexane gave the alcohol (38.5 g, 95%), mp 81.5–82 °C,  $\nu_{max}$  3370, 3040, 2920, 1610, 1470, 1220, 1160, 1050, 840, 770  $cm^{-1}$ . NMR:  $\delta$  2.0 (s, 2H), 4.54 (s, 2H), 5.02 (s, 4H), 6.52–6.56 (m, 3H), 7.32 (m, 10H).

3,5-Bis(benzyloxy)benzaldehyde (5). To a stirred mixture of pyridinium chlorochromate (40 g), sodium acetate (3 g) in anhydrous dichloromethane was added the alcohol (4) (38 g, 0.118 mol). After stirring for 1 h, it was diluted with dry ether (80 ml) and the dichloromethane-ether layer was decanted. The residue was washed with dry ether and the total organic layer was passed through silica-gel column. Removal of the solvent followed by crystallization with benzene-hexane furnished aldehyde (35.05 g, 93%) mp 76.5–77 °C,  $\nu_{max}$  3100–2830, 2740, 1690, 1600, 1460, 1390, 1350, 1260, 1220, 1160, 1085, 1060, 955, 910, 840, 735  $cm^{-1}$ . NMR:  $\delta$  4.96 (s, 4H), 6.64–7.28 (m, 13H), 9.72 (s, 1H).

1-[3,5-Bis(benzyloxy)phenyl]-1-pentanol (6). To a solution of butylmagnesium bromide (prepared from 30.14 g of butyl bromide and 5.76 g of magnesium) in anhydrous ether, was added aldehyde (5, 35.0 g, 0.11 mol) in anhydrous ether under  $N_2$  at 0 °C with stirring. It was stirred at room temperature for 2 h and then decomposed with 5%  $H_2SO_4$ . Organic layer was separated and the aqueous layer extracted with ether. The combined organic layer after washing with brine was stripped off the solvent and the residue was crystallized from acetone-benzene to give the alcohol (6) (38.1 g, 92%), mp 88 °C,  $\nu_{max}$  3420, 3085–3035, 2940, 2870, 1610, 1460, 1380, 1300, 1220, 1160, 1060, 910, 840, 735  $cm^{-1}$ . NMR:  $\delta$  0.88 (t, 3H), 1.28–2.08 (m, 6H), 4.64 (t, 1H), 4.96 (s, 4H), 6.48 (m, 3H), 7.28 (m, 10H).

5-Pentyl-1,3-benzenediol (Olivetol) (1). A solution of 1-[3,5-bis(benzyloxy)phenyl]-1-pentanol (6, 38 g, 0.1 mol), *p*-toluenesulfonic acid (0.6 g) in benzene (350 ml) was refluxed under Dean and Stark apparatus till no more water separated. It was washed with  $NaHCO_3$  and brine solutions. Solvent was evaporated and the residue was dissolved in ethanol (300 ml). It was hydrogenated with 10% Pd/C (1 g). After filtration, the solvent was evaporated to have a thick residue which was distilled under vacuum to procure olivetol (12.1 g, 66.7%). IR and NMR are in agreement with those reported for authentic sample.<sup>4d)</sup>

**References**

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