

A new route for scalable synthesis of 3,5 bis(hydroxymethyl)phenol and their derivatives

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Abstract- 3,5 bis(hydroxymethyl)phenol belong to the class polyphenols which is widely used for synthesis of complex nuclearity clusters and has clinical relevance in the treatment of allergies. It is a key organic compound widely used in the synthesis of various biologically active products, polymer chemistry and peptide chemistry. Mainly used in synthesis of poly(aryl ether)dendrimers and monodendrons and can also be used as an intermediate for synthesizing ligand and as a reagent for alkali metals.

Many literature methods are available for the synthesis of 3,5 bis(hydroxymethyl)phenol using lithium aluminium hydride (LAH) as a reducing agent. But these procedures are not suitable for scaleup due to safety concerns of LAH, tedious workup procedures and difficulty in isolation of product.

In this study, a simple and scalable approach for the synthesis of 3,5 bis(hydroxymethyl)phenol was proposed. Methyl ester of 5-hydroxy isophthalic acid was benzylated at the phenol group and reduced with sodium borohydride to obtain diol. The obtained benzylated compound was later debenzylated using Pd/C under H₂ conditions for desired product.

To study 3,5 bis(hydroxymethyl)phenol further, derivatives were made by methylation, reduction and bromination which yielded 3 derivatives.

3,5 bis(hydroxymethyl)phenol and the derivatives were analyzed using UV Visible spectroscopy, IR spectroscopy and NMR spectroscopy.

Keywords: 3,5 bis(hydroxymethyl)phenol, Scalable synthesis, Sodium borohydride, 5-hydroxy isophthalic acid, Key organic compound.

List Of Abbreviations

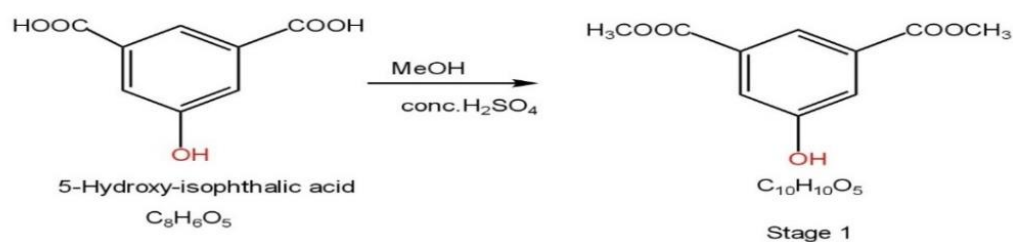
LAH	Lithium aluminium hydride
Pd/C	Palladium carbon
MeOH	Methanol
DMF	Di methyl formamide
THF	Tetra hydro furan
K ₂ CO ₃	Potassium carbonate
CH ₃ I	Methyl iodide
H ₂ SO ₄	Sulfuric acid
PBr	Phosphorous bromide
RBF	Round bottomed flask
NMR	Nuclear magnetic resonance
°C	Degrees
H ₂	Hydrogen
Conc.	Concentrated

NaH	Sodium hydride
%	Percentage
Da	Dalton
BF ₃ etherate	Boron trifluoride etherate

Experimental Work

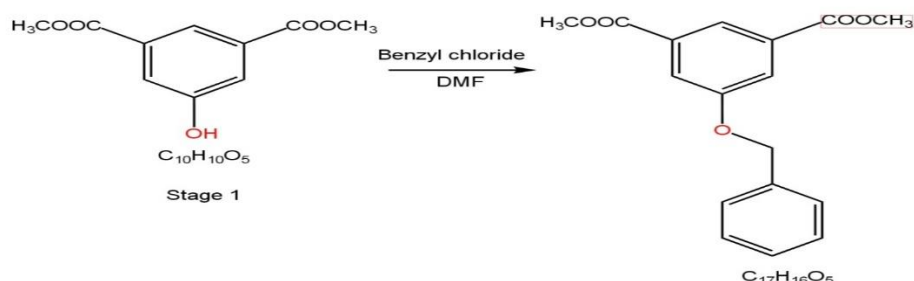
Stage 1

- 5-hydroxy isophthalic acid was taken as starting material for the synthesis of stage 1.
- 5-hydroxy isophthalic acid (100 grams), methanol (500 ml) was charged into RBF at room temperature and stirred at optimum speed. To the reaction mixture, slowly charged Sulfuric acid (16 ml) at room temperature. Temperature was raised to 70 °C and maintained the reaction mass at optimum speed for 15 hours. After completion of 15 hours, methanol was distilled out under vacuum and the compound was extracted with Ethyl acetate. Dried with sodium sulphate and distilled out under vacuum to obtain compound.



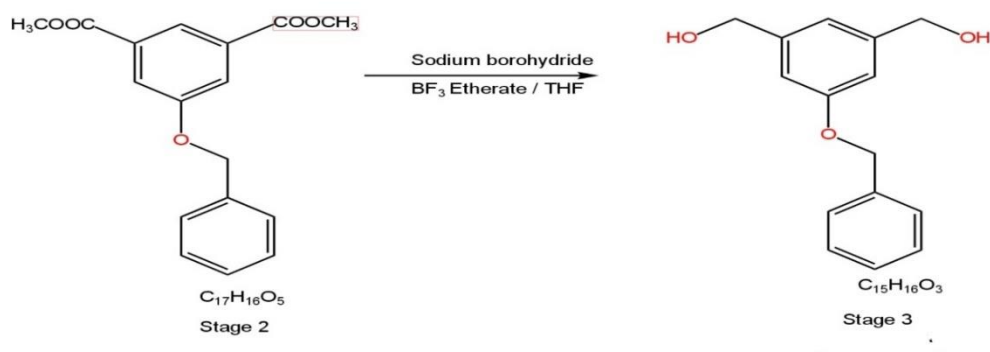
Stage 2

- 100 grams of Stage 1 is dissolved in DMF (500 ml) and Potassium carbonate (100 grams) was added into the RBF. Reaction is carried out with optimum stirring speed at room temperature. To the reaction mixture, Benzyl chloride (600 grams) is slowly charged at room temperature. Temperature of the reaction mass is raised to 80 °C and maintained for 15 hours. After the maintenance period, water (400 ml) is charged to the reaction mass. Formation of Solid was observed. Solid was filtered to obtain the compound



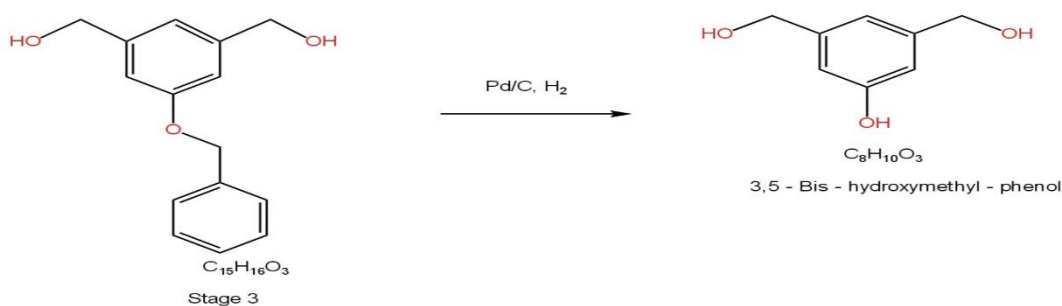
Stage 3

- Stage 2 (100 grams) and THF (1000 ml) was charged into RBF at room temperature. Reaction mixture was cooled to 0 °C. Lot wise added Sodium borohydride (210 grams) at 0 °C. Slowly added BF₃ etherate (692.5 grams) into the reaction mixture at 0 °C. Raised the temperature to 65 °C and maintained the reaction for 15 hours with optimum stirring speed. After the maintenance period, solvent was distilled out completely under vacuum. Solid formation was observed. To the reaction mass, sulphuric acid solution (10 %) was added slowly to acidify the reaction mass. Compound was extracted with ethyl acetate and dried with sodium sulphate. Solvent was distilled out completely and column chromatography with 70% ethyl acetate/hexane yields pure compound

**Stage 4**

Stage 3 (80 grams), 10% palladium carbon (8 grams) and methanol (800 ml) were charged into autoclave at room temperature. 6 kgs Hydrogen pressure was given and maintained the reaction for 10 hours. After 10 hours maintenance, reaction mass was filtered with the help of high flow under vacuum. Solvent was distilled out under vacuum to obtain the compound

- Yield obtained – 99.2%



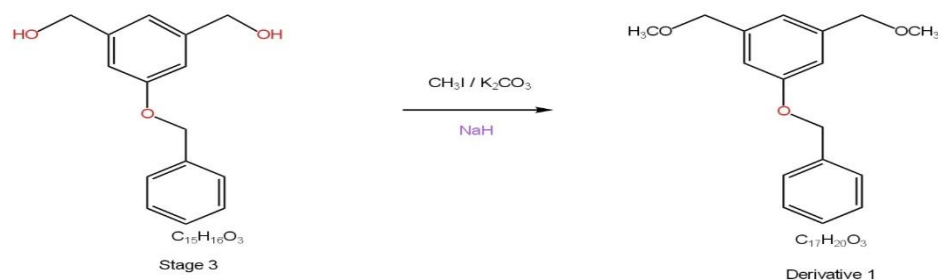
¹H NMR at 400 MHz in DMSO solvent showed chemical shift values (δ ppm) as follows : 4.38 (singlet, 2H), 4.39 (singlet, 2H), 5.043 – 5.046 (triplet, 2 – OH), 6.59 (singlet, 2H), 6.66 (singlet, 1H), 9.21 (singlet, -OH phenol)

Derivative 1

- Methylation:
- Sodium hydride (4.2 grams) along with DMF (100 ml) was charged into RBF under nitrogen atmosphere at 0 °C. Stage 3 (10 grams) was dissolved in DMF (100 ml) and slowly added into reaction mixture at 0 °C. Slowly charged methyl iodide (15 grams) at 0 °C. Reaction was maintained for 12 hours at room temperature with optimum stirring. After maintenance, slowly added 10% ammonium chloride solution to the reaction mass. Compound was extracted with ethyl acetate and dried with sodium sulphate. Compound was obtained by distilling out the solvent under vacuum

- Synthesized compound was found to be Benzyloxy 3,5-Bis (methoxymethyl)Benzene

- Yield – 88.5%

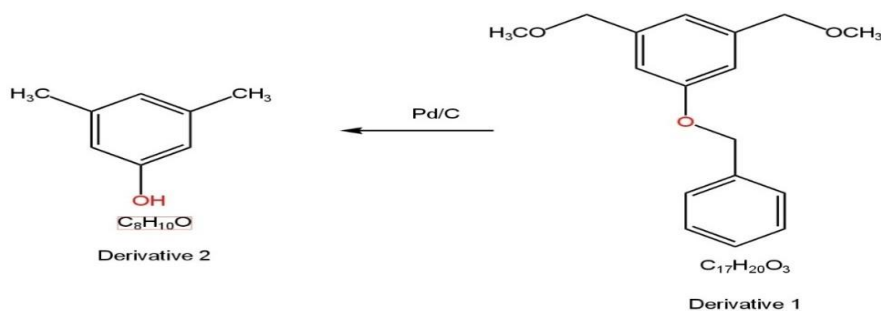


¹H NMR at 400 MHz in CDCl₃ solvent showed chemical shift values (δ ppm) as follows : 3.37 (singlet, 6H, 2 -OCH₃), 4.30 (singlet, 4H, 2 -CH₂), 5.07 (singlet, 2H), 6.40 (singlet, 3H), 7.31-7.30 (triplet, 1H), 7.36-7.33 (triplet, 2H), 7.44-7.42 (doublet, 2H)

Derivative 2

- De benzylation:
- Derivative 1 (10 grams), palladium carbon (1 gram) and methanol (200 ml) were charged in autoclave and given 5 kgs pressure. Reaction was maintained at room temperature for 48 hours. After maintenance, reaction mass was filtered under vacuum with high flow. Distilled out methanol under vacuum to obtain the compound. Synthesized compound was found to be 3,5-Dimethyl Phenol

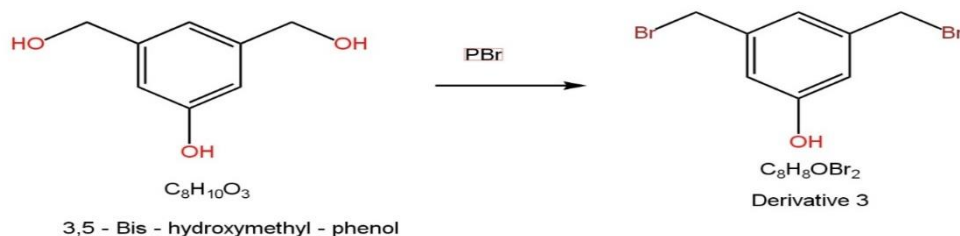
- Yield obtained – 93.3%



¹H NMR at 400 MHz in CDCl₃ solvent showed chemical shift values (δ ppm) as follows : 2.26 (singlet, 6H, 2 -CH₃), 6.46 (singlet, 2H), 6.57 (singlet, 1H)

Derivative 3

- Stage 4 (10 grams) was charged along with MDC (400 ml) at 0 °C
- Phosphorous bromide (15 grams) was slowly added into the reaction mixture at 0 °C. Temperature was raised to 37 °C and maintained for 14 hours. After 14 hours, the reaction mass was transferred into 10 % sodium bicarbonate solution. Compound was extracted with MDC and dried with sodium sulphate. Under vacuum distillation compound was obtained
- Synthesized compound was found to be 3,5-Bis (bromomethyl)Phenol
- Yield – 88.8%



¹H NMR at 400 MHz in CDCl₃ solvent showed chemical shift values (δ ppm) as follows : 4.40 (singlet, 4H, -CH₂), 6.81 (singlet, 2H), 6.97 (singlet, 1H)

Results And Discussion

- 3,5 bis(hydroxymethyl)phenol and their derivatives were synthesized.
- Methylation, Debenzylation and Bromination was performed using 3,5 bis(hydroxymethyl)phenol
- Synthesized derivatives were found to be Benzyloxy 3,5-Bis (methoxymethyl)Benzene, 3,5-Dimethyl Phenol and 3,5-Bis (bromomethyl)Phenol
- They were analyzed using ¹H NMR at 400 MHz in DMSO and CDCl₃ solvents
- % Yield of the compounds increased by this method of synthesis

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