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Regioselectivity in the preparation of 2-hydroxy-4-methoxy benzaldehyde from resorcinol

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Abstract

Three reactions, namely, Reimer–Tiemann reaction of resorcinol, one pot Reimer–Tiemann reaction of resorcinol and its methylation and finally Reimer–Tiemann reaction of resorcinol monomethyl ether were studied. Better selectivities were observed in the first two reactions when β-cyclodextrin (β-CD) and its derivatives were employed. The formation of 2,4-dihydroxybenzaldehyde and 2-hydroxy-4-methoxybenzaldehyde from the first two reactions showed better conversion than the control reaction. In the process, 70.0% 2,4-dihydroxybenzaldehyde was detected in the presence of 1 equivalent of β-CD and 48.2% 2-hydroxy-4-methoxybenzaldehyde was detected in the presence of 0.2 equivalent of HPβ-CD. However, Reimer–Tiemann reaction of resorcinol monomethyl ether resulted in only a marginal increase (43.9%) of 2-hydroxy-4-methoxybenzaldehyde (I) in the presence of 0.2 equivalent of β-CD as compared to the control (35.2%). The observed results were explained in terms of specific orientation of resorcinol inside the β-CD cavity which facilitates the attack of dichlorocbenzene from the narrower end on the electron rich ortho position to the –OH of resorcinol leading to the formation of 2,4-dihydroxybenzaldehyde or 2-hydroxy-4-methoxybenzaldehyde(I). © 2001 Elsevier Science B.V. All rights reserved.

Keywords: β-Cyclodextrin; Regioselectivity; Resorcinol; 2-Hydroxy-4-methoxybenzaldehyde

1. Introduction

2-Hydroxy-4-methoxybenzaldehyde (I) is a pleasant smelling aromatic aldehyde with a flavour note resembling vanillin, which is obtained both synthetically and naturally (from the cured pods of *vanilla planifolia*). 2-Hydroxy-4-methoxybenzaldehyde (I) is present in swallow roots (*Decalepis hamiltonii*, Wight and Arn.) which on steam distillation, yields about 0.8% of the compound [1]. It is also present to the extent of about 0.225% in roots of *Hemidesmus Indicus* (Indian Sarsaparilla) [1] and 0.26% in roots of *Tylophora indica* [2]. Use of compound I in skin cosmetics has been reported [3]. It has also been found that the compound can also be used as an antimicrobial agent [4], insecticidal agent [5] and as a pickle [2].

When substrates included inside cyclodextrin cavity are subjected to reaction by using suitable reagents, regio-specific products evolve due to selective direction of reagents to specific exposed regions of the included substrates [6]. This property is made use of in the preparation of I.

Although compound I is related to vanillin in structure and flavour note, this compound is not produced in large quantities on commercial scale like vanillin. In the present study, preparation of I was attempted using resorcinol. The following reactions were carried out in the presence of β-CD and

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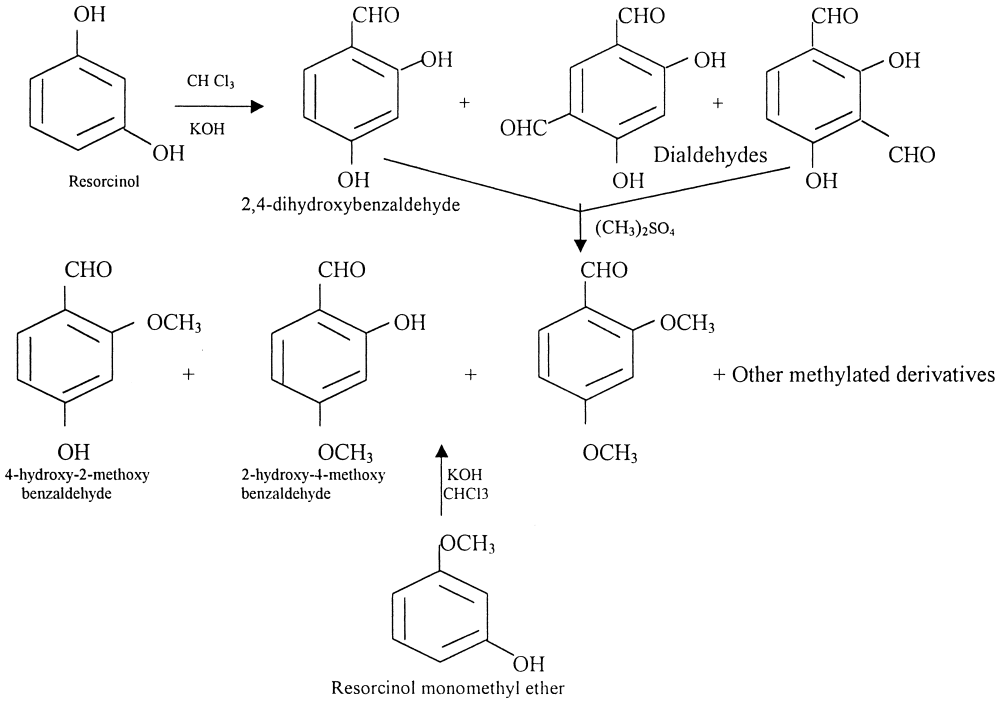


Scheme 1.

its derivatives namely hydroxypropyl-β-cyclodextrin (HPβ-CD), Heptakis-2,6-di-O-methyl-β-cyclodextrin (DMβ-CD) and β-cyclodextrin-epichlorohydrin polymer (β-CD polymer) (Scheme 1). These are: (i) Reimer–Tiemann reaction of resorcinol alone to prepare 2,4-dihydroxybenzaldehyde, (ii) one pot Reimer–Tiemann reaction of resorcinol followed by methylation and (iii) Reimer–Tiemann reaction of resorcinol monomethyl ether.

2. Results and discussion

2.1. Reimer–Tiemann reaction of resorcinol

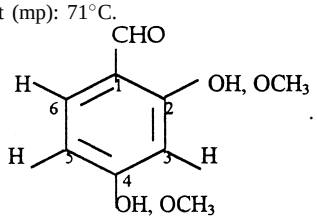
Reimer–Tiemann reaction of resorcinol yielded very little quantity of aldehydes, while several other side products like polymers, quinones and resorcinol degraded products were found to be formed in large amounts. The reaction was monitored by ^{1}H NMR. Measurement of area of aldehyde peaks around 8.5–10.5 ppm-enabled determination of conversion yields and proportion of aldehydic compounds formed (Table 1). The areas of aldehydes and aromatic protons were measured by tracing them on a uniform tracing paper and weighing them after careful cutting.

The control gave 40.4% aldehydes and 59.7% (Table 2) unreacted phenols and other products based upon the area of aromatic protons (other than those of the aldehydes). The yield of 2,4-dihydroxybenzaldehyde in the control was found to be <10.0%. Increase in concentration of β-CD resulted in increase in proportion of 2,4-dihydroxybenzaldehyde. Also, the conversion percentage, i.e. the proportions of total aldehydes formed were also found to increase accordingly. At 0.1 equivalent of β-CD, the total aldehydes formed was 40.8% out of which 2,4-dihydroxybenzaldehyde was 10.6% only, while at 0.2 equivalent of β-CD, 2,4-dihydroxybenzaldehyde formed was 28.4%. At 0.8 equivalents of β-CD, the total aldehydes formed corresponded to 61.3% of which 2,4-dihydroxybenzaldehyde was found to be 43.6%. Use of one equivalent of β-CD resulted in formation of 70.0% of 2,4-dihydroxybenzaldehyde with a total aldehyde content of 96.2%. At 0.5

Table 1
^{1}H NMR data of some selected products encountered in the Reimer–Tiemann reactions[a]

Groups	2,4-Dihydroxy-benzaldehyde[b] (ppm)	2-Hydroxy-4-methoxy-benzaldehyde[c] (ppm)	2,4-Dimethoxy-benzaldehyde[d] (ppm)	1,3-Dihydroxy benzene
CHO	9.71	9.72	10.22	–
2-OH	11.42	11.49	–	–
4-OH	5.97	–	–	–
1,3-OH	–	–	–	8.55
H-6	7.43	7.44; (8.7 Hz)	7.79; (8.7 Hz)	6.85 (m)[e]
H-5	6.50	6.55; (8.7 Hz, 2.2 Hz)	6.55; (8.7 Hz, 2.2 Hz)	7.0 (m)
H-4	–	–	–	6.35 (m)
H-3	6.39	6.44; (2.0 Hz)	6.44	
H-2	–	–	–	6.25 (m)
4–O–CH_3	–	3.84	3.86	
2–O–CH_3	–	–	3.88	

[a] Between 9.5–10.5 ppm several peaks corresponding to other dialdehydes and monoaldehyde other than those mentioned above were detected.
[b] Melting point (mp): 201–202°C.
[c] Melting point (mp): 40–42°C.
[d] Melting point (mp): 71°C.
[e] m: multiplets



equivalent of β-CD-polymer and DMβ-CD, the total percentages of aldehyde formed were 68.2 and 55.0, respectively. At 0.5 equivalent of DMβ-CD, 64.3% of 2,4-dihydroxybenzaldehyde was detected. In the presence of 0.2 equivalent of HPβ-CD, the total aldehydes formed was 42.7% out of which 56.4% was 2,4-dihydroxybenzaldehyde.

2.2. One pot Reimer–Tiemann reaction of resorcinol and methylation

An one-pot Reimer–Tiemann reaction of resorcinol and methylation of the products formed using dimethyl sulfate in the same reaction mixture was carried out in the presence of β-CD and its derivatives.

Table 2
Products from Reimer–Tiemann reaction of resorcinol

Conditions	2,4-Dihydroxy-benzaldehyde (%)	All aldehydes[a] (%)	Unreacted resorcinol and other products (%)
Control	<10	40.4	59.7
1:0.1 β-CD	10.6	40.8	59.2
1:0.2 β-CD	28.4	57.9	42.0
1:0.4 β-CD	[b]	51.5	48.5
1:0.8 β-CD	43.6	61.3	38.7
1:1 β-CD	70.0	96.2	3.8
1:0.5 β-CD-polymer	[b]	68.2	31.8
1:0.5 DMβ-CD	64.3	55.0	45.0
1:0.2 HPβ-CD	56.4	42.7	57.3

[a] Percentage of total aldehydes in the reaction mixture. Error in NMR measurments will be ±5%.
[b] Could not be measured accurately.

Table 3
Products from one-pot Reimer–Tiemann reaction of resorcinol followed by methylation[a]

Conditions	2-Hydroxy-4-methoxybenzaldehyde (%)	Other aldehydes + unreacted phenols
Control	12.5	77.5
1:0.1 β-CD	17.0	83.0
1:0.2 β-CD	16.8	84.0
1:0.4 β-CD	16.7	83.3
1:0.8 β-CD	21.4	78.6
1:1 β-CD	38.6	61.4
1:0.5 β-CD-polymer	25.4	74.6
1:0.5 DMβ-CD	9.3	90.7
1:0.2 HPβ-CD	48.2	51.8

[a] Error in NMR measurments will be ±5%.

The yield of I was found to be uniformly less in these reactions. The control gave only 12.5% (Table 3) of I. However, in all these reactions, there was formation of I. Yields of 17.0, 16.8, 16.7, 21.4, 38.6% I were achieved when 0.1, 0.2, 0.4, 0.8, and 1 equivalent of β-CD were employed. There was a yield of 48.2% of I with 0.2 equivalent of HPβ-CD. In the presence of 0.5 equivalent of DMβ-CD and β-CD-polymer, the yields of I were 9.3 and 25.4%, respectively. The reaction also gave several products, which included 6-hydroxy-2-methoxybenzaldehyde and 6-hydroxy-2-methoxybenzene-1,4-dialdehydes among other products. There was a gradual increase in the formation of I with increase in concentration of β-CD. However, 0.2 equivalent of HPβ-CD gave better yield of I (38.6%) than what was observed at a maximum concentration of 1 equivalent of β-CD employed.

2.3. Reimer–Tiemann reaction of resorcinol monomethyl ether

Resorcinol was methylated using dimethyl sulfate to get resorcinol monomethyl ether. The isolated monomethyl ether was then subjected to Reimer–Tiemann reaction. The results are shown in Table 4.

Here also, the formation of I was observed (Table 4). However, the yield of I was not found to be very much different from that of control (35.2%) when the reaction was carried out with β-CD and its derivatives. There was slight increase in the formation of I with increase in β-CD concentration upto 0.2 equivalent that decreased at higher β-CD concentration. With 0.1, 0.2, 0.4, and 1 equivalents of β-CD, the yields of I were 40.8, 43.9, 39.3, and 28.8%, respectively. With 0.2 equivalent of HPβ-CD, there was 15.4% yield of I. With 0.5 equivalent of β-CD-polymer and DMβ-CD, the yields of I were 30.2 and 14.5%, respectively.

Of the three reactions studied, namely, Reimer–Tiemann reaction of resorcinol, one-pot Reimer–Tiemann reaction of resorcinol followed by methylation and Reimer–Tiemann reaction of resorcinol monomethyl ether, better selectivities were observed in the first two reactions when β-CD and its derivatives were employed. The formation of 2,4-dihydroxybenzaldehyde and I from the first two reactions showed distinct increase in yields and good conversions than the control reaction. An yield of 70.0% 2,4-dihydroxybenzaldehyde was achieved in the presence of one equivalent of β-CD from the reaction (i) and 48.2% of I was achieved in the presence of

Table 4
Products from Reimer–Tiemann reaction of resorcinol monomethyl ether[a]

Conditions	2-Hydroxy-4-methoxy-benzaldehyde (%)	Other aldehydes + unreacted phenols
Control	35.2	64.8
1:0.1 β-CD	40.8	59.2
1:0.2 β-CD	43.9	56.2
1:0.4 β-CD	39.3	60.7
1:0.8 β-CD	[b]	[b]
1:1 β-CD	28.8	71.2
1:0.5 β-CD-Polymer	30.2	69.8
1:0.5 DMβ-CD	14.5	85.9
1:0.2 HPβ-CD	15.4	84.6

[a] Error in NMR measurements will be ±5%.
[b] Could not be measured accurately.

0.2 equivalent of HPβ-CD from the reaction (ii). However, Reimer–Tiemann reaction of resorcinol monomethyl ether resulted in only a marginal increase in I in the presence of 0.2 equivalent of β-CD.

These studies indicate specific orientation of resorcinol inside β-CD cavity during Reimer–Tiemann reaction. Inclusion of dichlorocarbene along with the phenol inside β-CD cavity has been reported [7–10]. Later, Maheswaran and Divakar 1997 [11] have indicated orientation of phenyl end of guaiacol and catechol inside β-CD cavity with –OH and $–OCH_3$ groups projecting outside. This orientation explained the selectivities observed in the Reimer–Tiemann reaction of guaiacol and catechol and hydroxymethylation of guaiacol [10,12]. In case of guaiacol and catechol the attack of dichlorocarbene *para* to –OH resulted in predominant formation of vanillin and protocatachuic aldehyde [12]. On the other hand, in the hydroxymethylation reaction, the attack of formaldehyde on the *para* position to $–OCH_3$ of guaiacol led to an enhanced formation of isovanillyl alcohol.

Such orientation of resorcinol or resorcinol monomethyl ether inside β-CD cavity should be responsible for the predominant formation of 2,4-dihydroxybenzaldehyde or I. Although orientation of phenyl end of resorcinol inside the cavity will be the most preferred geometric fit, the presence of OH group *meta* to OCH_3 (or OH) may result in the orientation as shown in Fig. 1. This orientation would explain the facile attack of dichlorocarbene included through the narrower end on the electron rich *ortho* position to –OH of included resorcinol or resorcinol monomethyl ether which gave rise to the above mentioned products in larger proportions.

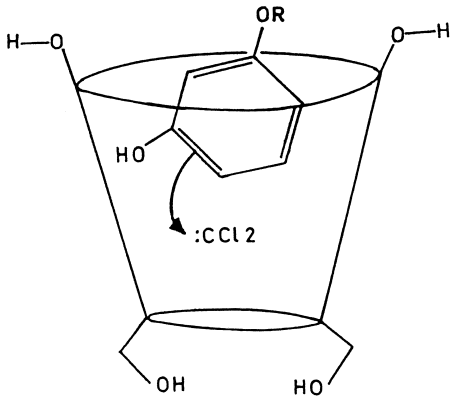


Fig. 1. Orientation of resorcinol molecule inside the β-cyclodextrin molecule. R = H, OCH_3.

The above three reactions employed in this study indicated that better yields will be obtained if 2,4-dihydroxybenzaldehyde was methylated with dimethyl sulfate separately. One-pot Reimer–Tiemann reaction of resorcinol and its methylation as well as Reimer–Tiemann reaction of resorcinol monomethyl ether gave reduced yields with cumbersome work up procedures. Therefore, the approach using β-CD and its derivatives offers an important route for selective formylation of resorcinol or selective methylation of 2,4-dihydroxybenzaldehyde.

3. Experimental

β-Cyclodextrin used was a gift from American Maize Products company, USA. β-CD-Polymer, DMβ-CD and HPβ-CD were prepared by the procedures of Shaw and Buslig 1986 [13], Szejtli et al. 1980 [14] and Pitha et al. 1981 [15], respectively, and were used in reactions. $CDCl_3$ and DMSO-d_6 procured from Sigma Chemicals Co. Ltd., dimethyl sulfate and resorcinol procured from SD Fine Chemicals Ltd. India, chloroform, diethyl ether, potassium hydroxide, sodium sulfate and butanol obtained from Qualigens India Ltd., and sodium bicarbonate from Ranbaxy Laboratories India were used.

3.1. Reimer–Tiemann reaction of resorcinol

Reimer–Tiemann reaction was carried out by stirring 0.25–2.5 g (0.22–2.2 mmol) β-CD or 1.5 g (1.127 mmol) DMβ-CD or 0.7 g (0.454 mmol) HPβ-CD or 1.7 g (1.333 mmol) β-CD-polymer along with 0.25 g (2.27 mmol) resorcinol at 60°C with 2.5 g (44.64 mmol) KOH in 10 ml water. Chloroform 0.7 ml (8.77 mmol) was added over a period of 7 h at 0.1 ml/h. The reaction was held at 60°C for a further period of 4 h. The work up procedure consisted of acidification of reaction mixture with dilute H_2SO_4, extraction with butanol, drying with sodium sulfate and distillation of butanol to get the final product. The reaction was monitored by ^{1}H NMR spectroscopy by dissolving the reaction mixture in $CDCl_3$/DMSO-d_6 solvent mixture. The area of aldehyde proton signals

was used in determining proportions of the products formed.

3.2. One-pot synthesis involving Reimer–Tiemann reaction of resorcinol and methylation

In case of one pot synthesis (continuous Reimer–Tiemann reaction and methylation) the procedure for Reimer–Tiemann reaction was followed as mentioned above and then methylation was carried out on the same reaction mixture by adding $(CH_3)_2SO_4$ (1.921 mmol) for a period of 2 h by maintaining the temperature at 80°C. The reaction mixture was continuously stirred for 10 h. After acidification of the reaction mixture with dilute H_2SO_4, the compounds were extracted in butanol, dried with sodium sulfate and butanol was evaporated to get a mixture of mono and dialdehydes (2,4-dihydroxybenzaldehyde, 2,6-dihydroxybenzaldehyde and 2,6-dihydroxy-1,4-benzene dialdehyde along with unreacted resorcinol).

3.3. Reimer–Tiemann reaction of resorcinol monomethyl ether

To resorcinol monomethyl ether (2.22 mmol) in 10 ml water, KOH (44.64 mmol) was added. Then, the procedure discussed for Reimer–Tiemann reaction for resorcinol with β-CD for 0.1, 0.2, 0.4, 0.8, and 1 equivalents and 0.5 equivalent for β-CD-polymer and DMβ-CD and 0.2 equivalents of HPβ-CD was followed and the reaction mixture after acidification was extracted with butanol, dried and evaporated to get a mixture of mono and dialdehydic methoxy resorcinols which were then analysed by ^{1}H NMR.

3.4. Preparation of resorcinol monomethyl ether

This compound was prepared according to the method by Bredereck and Henning [16]. To 5 g resorcinol (0.454 mol) in a three necked round bottomed flask containing 10 ml dichloroethane, 3.63 ml $(CH_3)_2SO_4$ (0.375 mol) (which was washed several times with $NaHCO_3$ solution and water until it was free from acid and distilled at 76°C at 15 mm) and 4 g (0.1 mol) NaOH (in 5 ml water) was added dropwise with stirring. The reaction mixture was then refluxed for about 2 h followed by stirring for 18 h. The mixture was maintained alkaline throughout the reaction. The reaction mixture was extracted with butanol, which was dried by sodium sulfate and distilled off to get the product. The product on recrystallisation with methanol gave resorcinol monomethyl ether 2.5 g (54%).

3.5. ^{1}H NMR spectroscopy

Brüker WH-270 NMR instrument operating at 270 MHz fitted with a Spectrospin magnet was employed for recording the NMR spectra. ^{1}H NMR spectra were taken with about 30–50 mg of the substance in 0.5 ml of $CDCl_3$. About 200 scans were accumulated to obtain a spectrum. The samples were recorded at 20°C with tetramethylsilane as an internal reference for measuring the chemical shift values to within ±0.01 ppm. A region from 0–15 ppm was scanned.

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