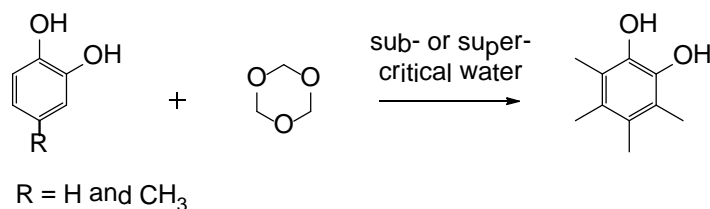


Simple, Non-catalytic Permethylation of Catechol Derivatives in Subcritical and Supercritical Water

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Abstract

Environmentally benign, non-catalytic, simple, and complete aromatic ring methylation of catechol derivatives by using 1,3,5-trioxane as the source of methyl groups was investigated in subcritical and supercritical water and under solvent-free conditions. Irrespective of the presence of subcritical and supercritical water as a reaction medium, catechol and 4-methylcatechol afforded the *permethylation* product 3,4,5,6-*tetramethylcatechol*. Only a small amount of 3,4,5,6-*tetramethylcatechol* (2% yield) was obtained under solvent-free conditions at 400 °C for 10 min. However, supercritical water considerably accelerated the formation of 3,4,5,6-*tetramethylcatechol* (13% yield) under the conditions of 400 °C, 10 min, and 0.35 g/mL water density.

1. Introduction

Aromatic ring methylation of catechol derivatives is an important process in organic synthesis because several methylcatechols are essential industrial intermediates [1–7]. To obtain ring-methylated catechols, the Friedel–Crafts reaction catalyzed by strong acids such as protic acids, Lewis acids, and solid acids is widely applied [8–12]. However, *permethylation* of the aromatic ring in catechols is a relatively difficult process because several steps are generally required even in the presence of a catalyst [13]. On the other hand, non-catalytic reactions in supercritical alcohols affording 2,6- and/or 4-methylated phenol derivatives have been reported as a new method for aromatic ring methylation of phenol derivatives [14]. In addition, non-catalytic methylation of hydroquinone, a structural isomer of catechol with two electrodonating hydroxyl groups, in supercritical methanol has been reported [15]; however, the reaction did not lead to *multimethylation*, but resulted in *monomethylation*. Thus, non-catalytic *multimethylation* of activated phenol derivatives such as catechol in supercritical fluids is not yet achieved.

Subcritical water (sub-CW) and supercritical water (SCW) have been used as new reaction media in organic transformations because of their unique properties such as large ion products, high solubility of organic materials, high density, and low viscosity [16–18]. Many important organic reactions such as secondary alcohol oxidation without an oxidant or a catalyst to generate carbonyl compounds and hydrogen gas [19], efficient non-catalytic Oppenauer oxidation of alcohols [20], and

the Beckmann rearrangement [21] have been performed under non-catalytic conditions in sub-CW and SCW. Regarding 2,6- and 4-alkylation of phenol in SCW, a pioneering work using aldehydes as a source of alkyl groups was reported by Adschiri et al.; 2,6- and 4-alkylation of phenol showed much higher reactivity than methylation of phenol using supercritical methanol [22–26]. Therefore, using a formaldehyde equivalent as the source of methyl groups for non-catalytic *permethylation* or *multimethylation* of catechol derivatives in sub-CW and SCW would be an alternative method.

In this paper, we report a new and efficient method for *permethylation* of catechol derivatives using 1,3,5-trioxane as a formaldehyde equivalent in the absence of a catalyst and in a very short reaction time under the high temperature and pressure conditions of sub-CW and SCW.

2. Material and methods

Catechol, 4-methylcatechol, and 1,3,5-trioxane were purchased from Nacalai Tesque Inc., and 2,4-xyleneol, 2,6-xyleneol, and salicyl alcohol were purchased from Wako Pure Chemical Industries Ltd. ^1H NMR spectra were obtained on a Varian Unity Inova spectrometer operating at 400 MHz. Gas chromatography-mass spectrometry (GC-MS) analyses were performed on a Shimadzu GCMS-QP 5050, and GC analyses were performed on a Shimadzu GC-17A gas chromatograph with CBP-5 and/or DB-1 columns.

The reagents and reverse osmosis water, into which N_2 gas was bubbled for 30 min to remove dissolved oxygen, were introduced in an SUS 316 batch type reactor (10 mL volume). The reactor was purged with N_2 for 10 min to remove oxygen and was sealed with a screw cap equipped with a thermocouple for measuring the inner reactor temperature. Then, the reactor was placed in a molten salt bath and heated at a controlled temperature for an appropriate duration. It took about 20–30 s to raise the inner reactor temperature to 300–420 °C. After the requisite reaction time, the reactor was placed into an ice water bath to quench the reaction. The reactor was allowed to cool to 0 °C before the screw cap was opened. The reaction mixture was extracted thrice with ethyl ether. The organic phase was separated and the solvent was evaporated *in vacuo* to obtain crude products. The crude products were purified by silica gel chromatography (Wakogel C-200, ether and hexane) and gel permeation chromatography (GPC) (JAI gel 1H and 2H, chloroform) if necessary. The products

were identified by comparing their ^1H NMR and GC-MS spectra with the reported and/or authentic sample spectra. Conversions of the reactants and yields of the products were determined using an internal standard method in the GC analysis; *n*-dodecane was used as an internal standard.

3. Results and discussion

3.1 Permethylation of catechol

As a preliminary experiment, simple catechol (**1**) (0.91 mmol) was treated with an excess amount of 1,3,5-trioxane (**2**) (3.00 mmol, 3.3 equiv. affording 10 equiv. of formaldehyde to **1** under the reaction conditions) [27,28] in sub-CW and SCW in a batch type reactor (10 mL volume) (Scheme 1). Although the reaction was performed under inert conditions using N₂-bubbled water under N₂ atmosphere, treatment of **1** with an excess amount of **2** in sub-CW and SCW produced black reaction mixtures. The black color can be ascribed to *o*-quinone from catechol (**1**) with some impurities. Nevertheless, with complete consumption of **1**, the permethylation product 3,4,5,6-tetramethylcatechol (**6**, 5%) was successfully obtained as the major product of the reaction with trace amounts of 3-methylcatechol (**3**, <0.5%), 3,6-dimethylcatechol (**4**, <0.5%), and 3,4,6-trimethylcatechol (**5**, <0.5%) in sub-CW at 350 °C for 10 min in the presence of 3.5 mL water. However, the products **3** (3%), **4** (3%), and **5** (2%) were obtained by reaction in the absence of water at 400 °C for 10 min. Considering the black color of the reaction mixture and the complete consumption of **1**, the low yields of the methylation products in this reaction could be attributed to the degradation of **1**, which is a common feature of organic compounds under such high-temperature conditions with inherent high energy.

Scheme 1.

Reaction of catechol (**1**) and 1,3,5-trioxane (**2**) in subcritical and supercritical water.

3.2 Permethylation of 4-methylcatechol

A monomethylated catechol, 4-methylcatechol (**7**), which is one of the simplest intermediates for the permethylation of **1**, was selected as an alternative. When **7** was treated under reaction conditions similar to those of **1** in sub-CW and SCW, the color of the reaction mixture was not black and permethylation product **6** and multimethylation products **5** and 3,4,5-trimethylcatechol (**8**) were obtained. In product **5**, two methyl groups were positioned adjacent to the hydroxyl groups on the benzene ring, and in **8**, one of the three methyl groups positioned adjacent to the hydroxyl groups (Table 1). To optimize the reaction conditions resulting in permethylation, temperature dependence was investigated for a fixed reaction time (10 min) and in the presence of a fixed amount of water (0.35 g/mL). While **6** was the sole product of the reaction, it was obtained in very low yield (3%) at a low temperature (300 °C). The yield of permethylation product **6** as well as the total yields of methylation products **5**, **6**, and **8** increased with the reaction temperature (Table 1, Entries 1–4). The highest yield of **6** (13%) was obtained at 400 °C (Table 1, Entry 4). Prolonged reaction improved the yield of **6** and it was almost saturated after 10 min at 380 °C and 0.35 g/mL water density (Table 1, Entries 5, 3, and 6). In addition, the total yields of the methylation products **5**, **6**, and **8** improved with increasing reaction time under the same conditions. Meanwhile, change in water density showed critical influence on the product distribution. In the absence of water, the reaction at 400 °C for 10 min predominantly afforded **5**, which bears two methyl groups adjacent to the hydroxyl groups on the benzene ring, with small amounts of **8** and permethylation product **6** (Table 1, Entry

7). The yield of *permethylation* product **6** and the total yield of methylation products **5**, **6**, and **8** increased with water density and saturated around the critical water density of 0.35 g/mL (Table 1, Entries 7, 8, 4, and 9). The low yield of solvent-free reaction can be a result of oligomerization of polymerization of the materials at high-temperature. Interestingly, change in water density did not affect the yield of **5**. Thus, water accelerated the methylation of **7** to produce *permethylation* product **6**. Recently, Horikawa et al. reported non-catalytic methylation of hydroquinone in supercritical methanol, and only the *monomethylation* product was obtained in the reaction [15]. To compare the methylation of catechol derivatives using aldehyde equivalent **2** with that using methanol, compound **7** was treated with an excess amount of methanol (10 equiv. to **7**) as the source of the methyl group in sub-CW (3.5 mL of water at 350 °C for 10 min) and SCW (0.35 g/mL water density at 400 °C for 10 min). Conversions of **7** were less than 1% and no methylation product was obtained in either reaction. These results clearly indicate that *permethylation* of catechol derivatives using **2** provides a much enhanced route than that using methanol in both sub-CW and SCW. The yield of *permethylation* product **6** is improved using a formaldehyde equivalent as the source of methyl group in sub-CW and SCW. Thus, we have demonstrated a relatively simple and facile method for *permethylation* of catechol derivatives.

Table 1

Reaction of 4-methylcatechol (**7**) and 1,3,5-trioxane (**2**) in subcritical and supercritical water.

3.3 Methylation of xylenols

To discuss the reaction pathways of catechol derivatives, phenol derivatives 2,4-xyleneol (**9**) and 2,6-xyleneol (**10**) were selected as simple compounds having only one unsubstituted position on the benzene ring (at the 4- and 6-position, respectively). In the reaction of **9** with an excess amount of **2** (3.3 equiv.) at 400 °C for 10 min under solvent-free conditions, the 6-position was methylated to afford 2,4,6-trimethylphenol (**11**) in moderate yield (17%) (Table 2, Entry 1). When the reaction was performed in SCW (400 °C, 10 min, and 0.35 g/mL water density), the yield of **11** considerably increased to 31% (Entry 2). In addition, 2-hydroxymethyl-4,6-dimethylphenol (**12**) (Figure 1) was obtained in 7% yield at the very beginning of the reaction under the conditions of 400 °C, 0 min, and 0.35 g/mL water density, suggesting that **12** should be a precursor of **11**. Actually, when salicyl alcohol (**13**), a homologue of **12**, was treated in SCW under similar conditions of 400 °C, 10 min, and 0.35 g/mL water density, 2-methylphenol and phenol were obtained as expected in 4 and 14% yields, respectively. In the case of **10**, where methyl groups blocked the 2- and 6-positions but the 4-position was unsubstituted, water played a key role in the reaction. In particular, 4-substituted product **11** was obtained in 12% yield in SCW (Table 2, Entry 4), but only a trace amount of **11** was obtained in the absence of water (Table 2, Entry 3). In conclusion, although water is indispensable for methylation at the 4-position, methylation at the 2- and/or 6-positions in phenol derivatives proceeded irrespective of the presence of water.

Table 2

Reaction of 2,4-xyleneol (**9**) and 2,6-xyleneol (**10**) with an excess amount of 1,3,5-trioxane (**2**) in supercritical water and under solvent-free conditions.

Fig. 1

Structures of 2-hydroxymethyl-4,6-*dimethylphenol* (**12**), salicyl alcohol (**13**), 6,6'-methylenebis(2,4-*dimethylphenol*) (**14**), and 4,4'-methylenebis(2,6-*dimethylphenol*) (**15**)

4. Reaction Pathway

Considering these results, the reaction pathway proposed by Adschiri et al. explains the *permethylation* of catechol derivatives demonstrated in this study [25]. Methylation of the 3- and 6-positions of catechol derivatives, which are adjacent to two OH groups, is more favorable than methylation at the non-adjacent 4- and 5-positions in the absence of water. This indicates that the 3- and 6-methylation of catechol derivatives proceeds via an “ene” reaction participated by adjacent OH groups, followed by keto-enol tautomerism resulting in 3-hydroxymethylation of the catechol derivative (intermediate I in Scheme 2, Pathway A). The hydroxymethylcatechol intermediate I can be converted into the corresponding 3-methyl products. Similar repeated reactions would afford 3,6-methylcatechol (Scheme 2, Pathway A). On the other hand, the fact that water promotes methylation at the 3- and 6-positions and triggers methylation at the 4- and 5-positions of catechol derivatives clearly indicates the existence of another reaction pathway; that is, a water-supported, H^+ -catalyzed Friedel–Crafts-type reaction at the 3-, 4-, 5-, and 6-positions (Scheme 2, Pathway B). In this reaction, formaldehyde and H^+ in SCW produce a hydroxymethyl cation, which causes hydroxymethylation via electrophilic substitutions at the 3- and 4-positions (intermediates I and III in Pathway B (a) and (b), respectively). In addition, both hydroxymethylcatechol intermediates, I and III, could react with another catechol to afford bis-compounds, II (or oligomers) and IV (or oligomers), by H^+ -catalyzed reaction in sub-CW and SCW, which suffer reductive cleavage to afford methylcatechol and catechol itself. Actually, when 4,4'-methylenebis(2,6-dimethylphenol) (**15**) was

treated in SCW (420 °C, 10 min, and 0.35 g/mL water density), bond fission occurred to give **10** and **11** in 37 and 26% yields, respectively. Repeated reactions would produce *permethylated* catechol in SCW. Adschiri et al. also mentioned similar alkylation of phenol with propionaldehyde to produce 2-propylphenol and 4-propylphenol [23,25]. However, the reaction mechanism is still not clear. As one of the possibilities, the reduction can be performed by nascent hydrogen generated by decomposition of formaldehyde, water gas shift reaction of carbon monoxide from decomposition of formaldehyde, and/or water catalyzed oxidation of alcohol moiety [19].

Scheme 2.

Reaction pathways of methylation of catechol in the absence of water and in subcritical or supercritical water.

5. Conclusions

Non-catalytic *permethylation* of catechol (**1**) and 4-methylcatechol (**7**) was performed with 1,3,5-trioxane (**2**) in sub-CW and SCW without any catalyst. The formation of the *permethylation* product 3,4,5,6-*tetramethylcatechol* (**6**) was observed in both reactions of **1** and **7**, and *permethylation* product **6** was obtained as the major product in these two reactions at 350 °C for 10 min in 3.5 mL water in the SUS 316 batch type reactor. The reaction of **7** showed temperature-dependence and time-dependence. Higher temperature and longer reaction time resulted in higher yield of *permethylation* product 3,4,5,6-*tetramethylcatechol* (**6**) as well as higher yields of the other methylation products 3,4,6-*trimethylcatechol* (**5**) and 3,4,5-*trimethylcatechol* (**8**). In the absence of water, only a small amount of *permethylation* product **6** (2%) was obtained at 400 °C for 10 min. However, the presence of water improved the formation of *permethylation* product **6**, which resulted in 11% and 13% yields at 380 and 400 °C, respectively, under the conditions of 10 min and 0.35 g/mL water density.

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