O-methylation of natural phenolic compounds based on green chemistry using dimethyl carbonate

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Abstract. The alkyl aryl ether compounds, of which methyl eugenol and veratraldehyde are the simplest intermediates can be synthesized by reacting eugenol and vanillin with the green reagent dimethyl carbonate (DMC). The reaction was carried out under mild of temperature and pressure. Excellent yields and selective products were obtained (95-96%) after a few hours. In the end of the reaction, the catalysts (base and Phase Transfer Catalyst) can be recovered and regenerated.

1. Introduction
The Green Chemistry principle [1] is a concept that aims to prevent pollution at the source, starting raw materials, synthesis procedure, the design process and the finished product before potential pollutants. It is important to replace the reagents that are toxic and harmful to the reagents that are safe and do not produce byproducts such as inorganic salts.

It is known that methylation reagents such as dimethyl sulfate or methyl halides are hazardous compounds. Dimethyl carbonate (DMC) is an alternative reagent that can be used in the methylation reaction to replace dimethyl sulfate or methyl halides [2, 3, 4]. In preparation of fragrances, dyes, and pesticides, or antioxidants in oils and fats or stabilizers of plastics, alkyl aryl ether compounds are needed [5, 6, 7].

Methylation of phenol with DMC performed in an autoclave at 160 °C using a base catalyst has been patented by Iori and Romano [8]. Several kinds of catalysts such as amines and a tertiary phosphine, penta alkilguanidin and cesium carbonate were used by Barcello et al., Lee and Shimizu [9, 10] in the reaction of phenolic compounds with dialkyl carbonates at temperatures between 120 to 200 °C with the autogenous pressure system. Bomben et al. [11] reported on the use of polyethylene glycol as solid-gas phase transfer and potassium carbonate as a base at high temperature. In this research, selective methylation at the hydroxy group in high yield was selected. However, the drawback of the procedure is hard to use because of the high boiling point is needed.

Ouk et al. [12] reported the methylation reaction with milder conditions where the methylation with DMC performed on the system solid-liquid phase transfer and the reaction was carried out at a temperature of 90-100 °C at atmospheric pressure. This reaction was used potassium carbonate as a base and tertbutyl amoniumbromida (TBAB) as PTC to give the best results on the methylation of p-cresol after a reaction time of 5 hours with a yield of 99%.
Eugenol and vanillin are a natural phenolic compound which are relatively abundant in Indonesia. As phenolic compounds, eugenol and vanillin can be converted into other compounds that are more useful with through the methylation reaction of eugenol to methyl eugenol and vanillin to veratraldehyde [13,14]. Research on the methylation of eugenol and vanillin have been reported [15]. Methylation reaction performed using DMS and PTC N- cetyl-N, N, N-trimethylammonium bromide (CTAB) for 2 hours at 29 °C. The product of methyl eugenol and veratraldehyde obtained with good yield. The disadvantage of this method is the DMS reagent is toxic and dangerous. To overcome these problems, we have studied the reaction of DMC with eugenol and vanillin under solid/liquid phase transfer conditions.

2. Experimental Detail
All chemicals used were of analytical grade from Merck and Co. Inc. include vanillin, methyl tertiary butyl ether (MTBE), dimethyl carbonate (DMC), potassium carbonate (K$_2$CO$_3$), hydrochloric acid (HCl), N-cetyl-N, N, N-trimethylammonium bromide (CTAB), tetrabutylammonium bromide (TBAB), polysorbate 80, and sodium sulfate anhydrous (Na$_2$SO$_4$). The substrate with laboratory grade is eugenol with 98.89% of purity. The instrument used in this study include infrared spectrophotometer (FT-IR, Shimadzu Prestige-21), Gas Chromatograph - Mass Spectrometer (GC-MS, Shimadzu QP-2010s, Rastek RXi-5MS, FID) and Gas Chromatography (GC, Hewlett Packard 5890, HP 5, FID).

Synthesis of methyl eugenol and veratraldehyde were carried out by refluxing eugenol or vanillin, DMC, K$_2$CO$_3$ and PTC for 5 hours. At the end of the reaction, the base (K$_2$CO$_3$) was recovered by filtration and the PTC was separated by extraction with an aqueous hydrochloric acid (until pH 1) and methyl tertiary butyl ether (MTBE). The organic phase, containing products, were evaporated with a rotary evaporator and analyzed by gas chromatography. In order to optimize the yield of the reaction the PTC/DMC/reaction time ratio and catalyst system were modified. The PTC recovered in the aqueous phase can be regenerated [16].

3. Results and Discussion

3.1. Methylation by varying of phase transfer catalyst
The results of methylation of eugenol and vanillin with CTAB, TBAB and Tween 80 as PTC via GC analysis are shown in table 1.

| Substrate | DMC (mmol) | PTC | Catalyst (mmol) | Time (h) | Yield (%) | Purity (%) |
|-----------|------------|-----|-----------------|----------|-----------|------------|
| Eugenol   | 16         | CTAB| 0.6             | 5        | 96.94     | 98.61      |
|           | 16         | TBAB| 0.6             | 5        | 92.65     | 94.24      |
|           | 16         | Tween 80 | 0.6            | trace   |           |            |
| Vanillin  | 16         | CTAB| 0.6             | 5        | 19.10     | 19.51      |
|           | 16         | TBAB| 0.6             | 5        | 38.50     | 38.81      |
|           | 16         | Tween 80 | 0.6         | trace   |           |            |

By looking at the yield and purity were not significantly different between using CTAB and TBAB as PTC for O-methylation of eugenol (Table 1). If compared with O-methylation of vanillin, using TBAB give better yield than CTAB, 19.10% when using CTAB and raised to 38.50% of yield when using TBAB. Therefore, tetrabutylammonium bromide (TBAB) was selected as PTC and used in the subsequent reaction. Selection of TBAB referred to one of the principles of green chemistry, which is to reduce the waste generated.
3.2. Methylation by varying the amount of dimethyl carbonate

The results of methylation of eugenol and vanillin with a variation of DMC via GC analysis are shown in table 2.

| Substrate       | PTC | Catalyst (mmol) | DMC (mmol) | Time (h) | Yield (%) | Purity (%) |
|-----------------|-----|-----------------|------------|----------|-----------|------------|
| Eugenol         | TBAB| 0.6             | 8          | 5        | 52.57     | 55.06      |
| "              | "   | 0.6             | 12         | 5        | 75.36     | 79.85      |
| "              | "   | 0.6             | 16         | 5        | 91.59     | 94.24      |
| Vanillin        | "   | 0.6             | 16         | 5        | 38.50     | 38.81      |
| "              | "   | 0.6             | 24         | 5        | 48.20     | 48.43      |

The results showed that the optimum concentration used in the methyl eugenol synthesis and veratraldehyde synthesis using DMC were 16 and 24 mmol. The use of DMC classified as excess. This is possible in addition to functioning as a methylation reagent, DMC also serves as a solvent. This fact is shown in table 2, where increasing concentrations of DMC further improve the yield and purity of product.

3.3. Methylation by varying the amount of phase transfer catalyst

The results of methylation of eugenol and vanillin with a variation of PTC’s amounts via GC analysis are shown in table 3.

| Substrate       | PTC | Catalyst (mmol) | DMC (mmol) | Time (h) | Yield (%) | Purity (%) |
|-----------------|-----|-----------------|------------|----------|-----------|------------|
| Eugenol         | TBAB| 0               | 16         | 5        | 0         | 0          |
| "              | "   | 0.2             | 16         | 5        | 59.73     | 62.91      |
| "              | "   | 0.4             | 16         | 5        | 96.22     | 99.00      |
| "              | "   | 0.6             | 16         | 5        | 91.59     | 94.24      |
| Vanillin        | "   | 0               | 24         | 5        | trace     | -          |
| "              | "   | 0.2             | 24         | 5        | trace     | -          |
| "              | "   | 0.4             | 24         | 5        | trace     | -          |
| "              | "   | 0.6             | 24         | 5        | 48.20     | 48.43      |

The yield of methyl eugenol is not significantly different on the use of 0.4 mmol or 0.6 mmol of PTC. Therefore, referring to the principles of green chemistry is the efficient use of chemical reagents, the selected amount of the PTC is 0.4 mmol. This was not followed by a veratraldehyde synthesis were not obtained good results when the amount of the catalyst is under 0.6 mmol.

3.4. Methylation by varying the reaction time

When the reaction time was increased from 2 hours to 3 hours, the yield of methyl eugenol increased significantly almost twice, being 96.16% with 99.37% of purity. At the vanillin, there is a significant difference that the reaction time takes longer than eugenol, almost twice. Therefore, it is determined that the optimal reaction time for the methylation reaction using dimethyl carbonate are 3 hours for yielded methyl eugenol and 10 hours for yielded veratraldehyde. The optimum reaction time via GC analysis shown in table 4. In comparison, the reaction time of veratraldehyde synthesis is longer than methyl eugenol synthesis.
Table 4. Effect of various reaction time on the yield

| Substrate | PTC | Catalyst (mmol) | DMC (mmol) | Time (h) | Yield (%) | Purity (%) |
|-----------|-----|-----------------|------------|----------|-----------|------------|
| Eugenol   | TBAB| 0.6             | 16         | 1        | 21.75     | 24.98      |
| "         | "   | 0.6             | 16         | 2        | 54.91     | 59.97      |
| "         | "   | 0.6             | 16         | 3        | 96.16     | 99.37      |
| "         | "   | 0.6             | 16         | 4        | 92.38     | 95.61      |
| "         | "   | 0.6             | 16         | 5        | 91.59     | 94.24      |
| Vanillin  | "   | 0.4             | 16         | 3        | 96.12     | 99.33      |
| "         | "   | 0.6             | 24         | 5        | 48.20     | 48.43      |
| "         | "   | 0.6             | 16         | 10       | 85.47     | 86.51      |
| "         | "   | 0.6             | 24         | 10       | 95.23     | 95.41      |

Figure 1. IR-spectra for veratraldehyde (a) and methyl eugenol (b)

Structure elucidation of methylation products from optimum methods were performed by means of IR (figure 1), GC (figure 2) and MS (figure 3). For methyl eugenol, IR (neat) : 3070, 2931, 2831, 1512, 1589, 1458 and 1033 cm⁻¹. The molecular formula was determined to be C₁₁H₁₄O₂ based on MS data (M⁺, calculated for being 178). For veratraldehyde, IR (neat) : 3194, 2954, 2846, 2731, 1689, 1600,
1400, and 1300 cm\(^{-1}\). The molecular formula was determined to be C\(_9\)H\(_{10}\)O\(_3\) based on MS data (M\(^+\), calculated for being 166).

![Figure 2](image1.png)  
**Figure 2** Chromatogram for veratraldehyde (a) and methyl eugenol (b)

![Figure 3](image2.png)  
**Figure 3** Mass spectra for veratraldehyde (a) and methyl eugenol (b)

Other research by Ouk et. al. [12] reported methylation of p-cresol with DMC takes 5 hours. Shieh et. al. [17] reported methylation of p-chlorophenol with DMC takes 16 hours (table 5). The different reactivity between phenolic compounds can be explained by the inductive effect of aldehyde group at the vanillin, halide group at p-chlorophenol, an alkyl group at p-cresol and allyl group in eugenol (Figure. 4).
Table 5. Effect of functional groups on the methylation reaction with DMC

| Substrate          | Functional Group Properties | Reaction time (hours) |
|--------------------|-----------------------------|-----------------------|
| Eugenol<sup>a</sup> | Electron Donating           | 3                     |
| p-Kresol<sup>b</sup> | Electron Donating           | 5                     |
| Vanillin<sup>c</sup> | Electron Withdrawing        | 10                    |
| p-chloro-phenol<sup>d</sup> | Electron Withdrawing      | 16                    |

Figure 4 (a) Vanillin; (b) Eugenol; (c) p-Cresol; (d) p-Chloro-Phenol

Aldehyde group at the vanillin and halide group at p-chlorophenol are electron withdrawing groups while the allyl group on eugenol and alkyl groups on p-cresol are electron donating groups. The existence of electron withdrawing groups will cause electron density at the OH-group (at vanillin and p-chlorophenol) will be reduced, so the ability of nucleophiles would be reduced. It makes the reaction will be more difficult and takes a long time. The opposite occurs in eugenol and p-cresol, where the electron donating groups will increase the electron density of OH groups. The ability of nucleophile will increase, the reaction will easily occur and takes a short time. The possible mechanism of this reaction is shown in figure 5.

Figure 5. The possible mechanism of methylation of Eugenol (a) and Vanillin (b) using DMC and PTC.
4. Conclusion
In conclusion, we have presented optimum conditions of the methylation reaction of eugenol and vanillin by using DMC as the environmental friendly reagent. The reaction was conducted under reflux conditions at 90 °C and obtained in 95–96% yield. Furthermore, the base and PTC which act as catalysts can be recovered and regenerated easily.

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