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# Mesyl guaiacol: a versatile intermediate for the synthesis of 5-aminomethyl guaiacol and related compounds

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**Abstract**—An original synthetic pathway for the preparation of 5-substituted guaiacol derivatives is described. This method relies on the deactivation of the phenol group by converting it into the corresponding mesyl ester. Amidomethylation reactions lead to regioselective C–C bond formation at the 5-position of guaiacol. Thus, 5-aminomethyl-guaiacol was obtained in four steps and 75% overall yield. © 2002 Published by Elsevier Science Ltd.

Functionalized aromatic compounds are key intermediates for the production of drugs,[1] pesticides,[2] natural products,[3] and polymers.[4] Guaiacol derivatives, for example, are very useful and versatile intermediates produced in more than one million metric tons per year. One of the most important compounds of this family is vanillin, 4-formyl-guaiacol, which is used in large quantities as a flavoring agent in the food industry. Other 4-substituted-guaiacol derivatives are easily prepared by classical Friedel–Crafts[5] chemistry or starting directly from the commercially available vanillin.

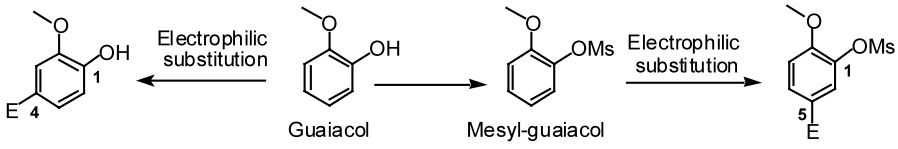
In contrast, 5-substituted guaiacol derivatives are more difficult to prepare, since the electrophilic substitution of guaiacol takes place predominantly at the 4-position[6] because of the strong directing effect of the hydroxyl group (Scheme 1).

Increasing demand for isoguaiacol derivatives justified the investigation of a new route for the synthesis of this family of regioisomers.[7]

Previous work on guaiacol showed that *para*-substitution at the 4 position is predominant under either basic or acidic conditions.[8] We envisioned that deactivatation of the phenol functionality would magnify the *para*-directing effect of the methoxy substituent and direct substitution specifically to the 5-position. Therefore, we undertook an evaluation of a series of deactivating groups. The acetate, trifluoroacetate, methylcarbamate, ethylcarbonate, and mesylate guaiacol derivatives were easily obtained in moderate to good yields (Table 1). The stability of these derivatives was tested under both mild and strong acidic conditions that are usually involved in electrophilic aromatic substitution processes.

In a 9:1 acetic acid/sulfuric acid mixture, both the acetate and trifluoroacetate groups were removed within a few hours at room temperature. In contrast the carbamate, carbonate, and mesylate groups proved to be stable.

In a 1:1 acetic acid/sulfuric acid mixture, both carbonate and carbamate derivatives decomposed with a half-life of about 4 h. The mesylate however was found to be indefinitely stable. In the same media, at 80°C, both




**Scheme 1.** Regioselectivity of the electrophilic substitution on the guaiacol and the corresponding mesylate.

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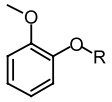
**Table 1.** Synthesis of the different protecting groups on the guaiacol

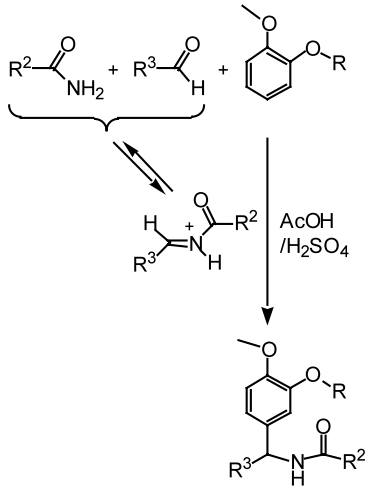


| R = | $SO_2Me$ | $CO_2Et$ | CONHMe | COMe | $COCF_3$ |
|---|---|---|---|---|---|
| Yield (%) | 95 | 95 | 60 | 95 | 50 |

the carbonate and the carbamate derivatives were completely degraded within 5 h, whereas the mesylate still showed a remarkable stability. In order to validate the assumption that introduction of electron-withdrawing groups on the phenol would reverse the regioselectivity of the electrophilic substitution, the above-described derivatives were subjected to amidomethylation. This one-pot process combines an amide, an aldehyde, and an aromatic substrate that is comparable to an aromatic version of the Mannich reaction[9] (Scheme 2).

In this reaction, an *N*-acylimine intermediate is formed by condensation of the aldehyde and the amide. Under the strongly acidic conditions, the latter is protonated to yield a highly reactive iminium ion, which subsequently reacts with electron-rich aromatic substrates.[10]

Guaiacol derivatives were subjected to amidomethylation conditions using 2 equiv. of acetamide, 1 equiv. of aldehyde at 80°C for 6 h in a 2:3 sulfuric acid/acetic acid mixture. Interestingly, the reaction proved to be highly regioselective with the mesyl guaiacol. Only the desired isomer was isolated in 90% yield, without formation of any side-product. With the acetate, trifluoroacetate, carbonate, and carbamate derivatives, the desired products were obtained only in trace amounts. These results agree with the stability experiments, where these substrates are rapidly deprotected under such strongly acidic conditions. The resulting free guaiacol then undergoes electrophilic substitution at the 4-position (Table 2).



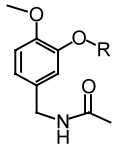

**Scheme 2.** The amidomethylation reaction.

Selective removal of the mesyl group was achieved by refluxing the substrate for 6 h in a 1:2 mixture of isopropanol/5% aqueous potassium hydroxide solution. After extraction with dichloromethane, the free phenol was obtained in 98% yield. Further refluxing in a 2N hydrochloric acid solution resulted in the formation of the desired bis-deprotected products. Selective hydrolysis of the acetamide could also be achieved in 95% yield by heating the substrate in concentrated hydrochloric acid. (Scheme 3).

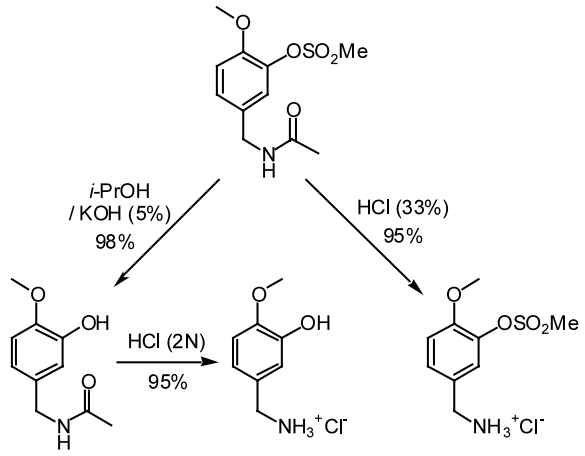
Interestingly, the yield of the demesylation step depends on the nature of the alcohol used in the solvent mixture. The most satisfactory results were obtained with a 1:2 mixture of isopropanol and water containing 5% KOH. Under these conditions no by-products were detected (Scheme 4).

It should be emphasized that a wide variety of 5-substituted guaiacol derivatives are accessible through this process by varying both the amide ($R^2$) and the aldehyde ($R^3$) functionalities.[11] Activated aldehydes, such as glyoxylic acid or 4-trifluorobenzaldehyde gave *iso*-substituted derivatives in more than 75% yield. It seems that there are no restrictions concerning the nature of the amide side-chain ($R^2$) as long as it is stable to the harsh acidic conditions. Hence, alkyl, aryl, and heteroaryl substituted amides afforded the condensation

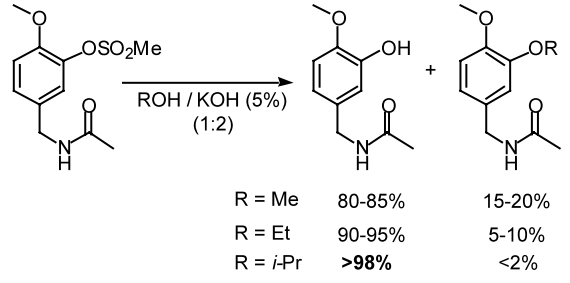
**Table 2.** Yield of the acetamidomethylation reaction



| R = | $SO_2Me$ | $CO_2Et$ | CONHMe | COMe | $COCF_3$ |
|---|---|---|---|---|---|
| Yield (%) | 90 | 12 | 9 | 4 | No product |




**Scheme 3.** Synthesis of 5-aminomethyl guaiacol derivatives.




**Scheme 4.** Influence of the solvent on the demesylation step.

products in high yield. Interestingly, the replacement of the amide by a methylcarbamate led to the corresponding *N*-alkoxy carbonyl protected amine in more than 80% yield.

In summary, we have developed an original synthetic pathway for the preparation of 5-substituted guaiacol derivatives. This method relies on masking the phenol into a deactivating group by converting it into the corresponding mesyl ester. Amidomethylation leads to the regioselective C–C bond formation at the guaiacol 5-position. Thus, 5-aminomethyl-guaiacol was obtained in a four-step sequence and 75% overall yield. Extension of this efficient method to the synthesis of 5-substituted guaiacol derivatives using various amides, carbamates, and aldehydes allows access to a wide range of *N*-benzyl amides and carbamates. Moreover, it shows that this original process involves inexpensive and readily available starting materials, such as acetamide, paraformaldehyde, guaiacol, methanesufonyl chloride, acetic and sulfuric acids, and can thus be carried out on a kg scale without any difficulty.

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