The Austrian Journal of Technical and Natural Sciences, No 7–8
ISSN 2310-5607

PREMIER Publishing
ppublishing.org

DOI:10.29013/AJT-24-7.8-18-21

SYNTHESIS OF METHYL ESTERS OF GALLIC ACID AND ITS DERIVATIVES

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Cite: *Kadirova Sh. O., Yuldasheva M. R., Abdumannopova N. B. (2024). Synthesis of methyl esters of gallic acid and its derivatives. Austrian Journal of Technical and Natural Sciences 2024, No 3–4.* https://doi.org/10.29013/AJT-24-7.8-18-21

Abstract

The article presents information on the method for obtaining esters of gallic acid, syringic acid and 3,4,5-trimethoxybenzoic acid with methanol and the analysis of compounds by IR, 1H and 13C NMR spectroscopy.

Keywords: *Gallic acid, syringic acid, 3,4,5-trimethoxybenzoic acid, methanol, ester*

Introduction

Gallic acid derivatives are commonly found in plants and fruits in nature, and they are currently utilized by humans either directly or indirectly as food products and medicinal substances. These derivatives have been used for various purposes such as treating depression, cancer, microbial infections, and lipid-dependent diseases, as well as exhibiting anticarcinogenic, antimicrobial, antimutagenic, antiangiogenic, and anti-inflammatory properties.

Recent data have shown that alkyl gallates are widely used as antioxidants in the food and cosmetic industries. Furthermore, derivatives of gallic acid, a major component of plant metabolism, are used as raw materials for ink, dye, and colorant manufacturers (Mahmoud N. N., Carothers A. M., Grunberger D., Belinski R. T., Churchill M. R., Martucci C., Newmark H. L., 2000). Pharmacological studies on these compounds have demonstrated that 3,4,5-trihydroxybenzoic acid and its derivative esters possess numerous therapeutic properties, including antioxidant, antifungal, antibacterial, antitumor, antiviral, and antiherpetic effects. There is a growing interest in the antioxidant activity of alkyl gallates due to their ability to absorb and reduce the formation of reactive oxygen species. As a result, scientific studies on gallic acid and its derivatives are being conducted globally, yielding excellent results (Choubey S. et al., 2015; URL: https://doi.org/10.4155/ppa.15.14;

Mahmoud N. N., Carothers A. M., Grun berger D., Belinski R. T., Churchill M. R., Martucci C., Newmark H. L., 2000; URL: https://asianpubs.org/index.php/ajchem/article/view/5556; Kubo, N. Masuoka, P. Xiao and H. Haraguchi, J., 2002; Weetall H. H., 1985; Badhani B., Sharma N., Kakkar R., 2015; Shi Z., 2015; URL: http://dx.doi.org/10.14233/ajchem.2015.17906; Fer

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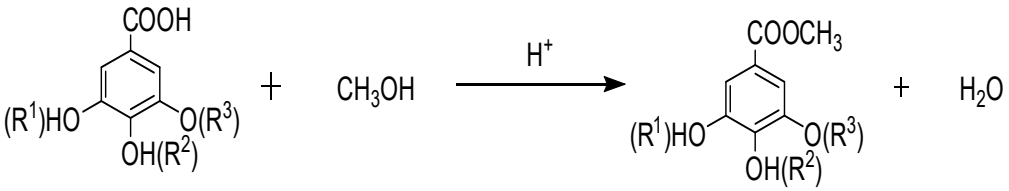
Gallic acid is a sensitive derivative that is prone to oxidation, therefore it is important to synthesize its ethers through chemical synthesis via fermentative methods. However, this method has several drawbacks including low yield, prolonged processing time, the requirement for specific solutions, and so on (Weetall H. H., 1985; Badhani B., Sharma N., Kakkar R., 2015).

Gallic acid and its derivative esters are known for their strong antioxidant properties. Scientific data highlights the significance of developing natural products based on them. These natural products or their derivatives, with potent antioxidant effects, can help reduce oxidative stress in cells and can also be used as building blocks for creating new drugs to prevent various diseases (Shi Z. et al. 2015; URL: http://dx.doi.org/10.14233/ajchem.2015.17906; Fernandes., Salgado. Gallic Acid: 2016; Citation: Zheng, Y., Geng, Y., Hou, W., Li, Z., Cheng, C., Wang, X., Yang, Y., 1996. URL: https:// doi.org/10.3390/molecules29091996; Fernandes, Salgado. (2015); Kadirova Sh., Yuldasheva M., Komilov K., Rakhimov R.; Yuldasheva M., Kadirova Sh., 2023. URL: https: //www.scholarexpress. net).

Alkyl gallates can be produced by boiling the corresponding acids with alcohols in the presence of various catalysts. Catalysts such as sulfuric acid, hydrogen chloride, boron trifluoride, aluminum chloride, trifluoroacetic anhydride, polyphosphate esters, neodymium oxide, dicyclohexylcarbodiimide, graphite, and bisulfate are commonly used. Toluene is typically used as a solvent in the synthesis of alkyl gallates, and the reactions are carried out with heating for 8–12 hours (Kubo, N. Masuoka, P. Xiao and H. Haraguchi, J. 2002).

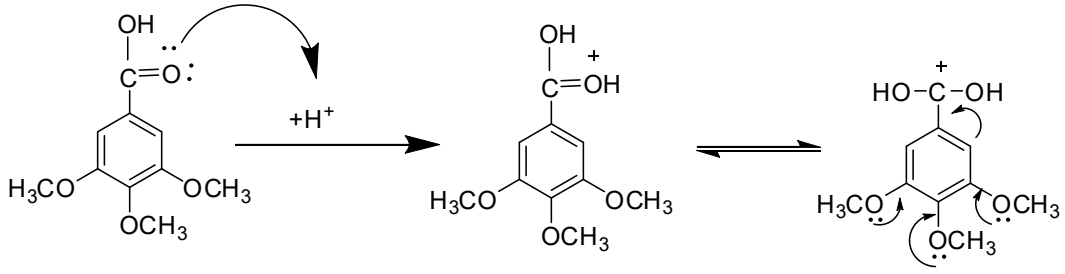
Results and discussion:

The esterification of gallic acid, syringic acid, and 3,4,5-trimethoxybenzoic acid with methanol using a sulfuric acid catalyst was conducted at the boiling point of the molar amount of methanol. The study investigated the impact of catalyst concentration, temperature, and molar ratio of reagents on the reaction efficiency. In the esterification reaction, the highest product yield was observed for hydroxybenzoic acid. The reaction equation is as follows:



1 = R^1, R^2, R^3 = H; 2 = R^1, R^2, R^3 = CH_3; 3 = R^1, R^3 = CH_3, R^2=H.

The ability of aromatic carboxylic acids to undergo esterification increases in the following order: gallic acid (78%), syringic acid (84%), 3,4,5-trimethoxybenzoic acid (89%). The high yield of the product in the reaction of methanol with 3,4,5-trimethoxybenzoic acid is due to the stabilization of the carbocation formed as a result of proton addition from the catalyst to the carboxyl group, facilitated by the action of the trimethoxy group.



The reaction is catalyzed by sulfuric acid, which protonates the carboxyl oxygen of gallic acid. Then, the electron-deficient carbon undergoes nucleophilic attack by methanol, resulting in a tetrahedral intermediate. Removing a water molecule from the tetrahedral intermediate leads to the formation of an ester. This reaction mechanism can be expressed as follows.

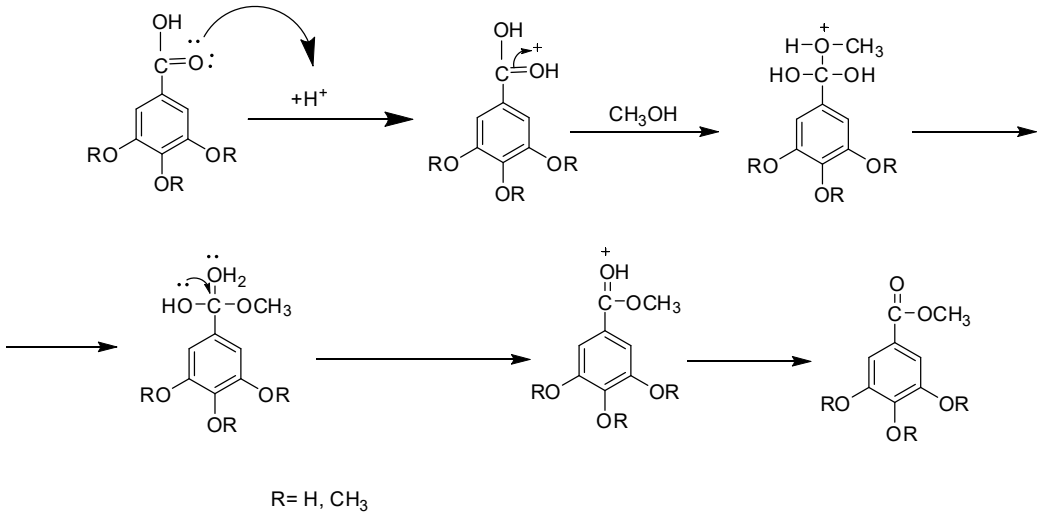


Table 1. *Physical quantities of gallic acid, syringic acid and 3,4,5-trimethoxybenzoic acid*

№	Temperature, °C	Duration of the reaction, hours	Product T(liquid)	Yeild %	Rf
1	68	10	202–203 °C	78	0.75
2	68	10	204–205 °C	84	0.40
3	68	10	168–169 °C	89	0.5

Experimental part: Synthesis of methyl gallate (**1**) 2 g (0.001 mol) of gallic acid and 25 ml (0.78 mol) of methyl alcohol, as well as 3–4 drops of sulfuric acid, were heated in a round-bottomed flask equipped with a reflux condenser. The reaction mixture was heated under reflux for 10 hours. The resulting substance was monitored every hour using TLC. After the reaction was complete, excess alcohol was removed and the residue was washed first with cold water and then with a 5% Na_2SO_4 solution. The white precipitate that settled at the bottom of the vessel was isolated through filtration and recrystallized using ethyl alcohol. Methyl ester of syringic acid and methyl ester of 3,4,5-trimethoxybenzoic acid were also synthesized using this method.

Melting point and thin-layer chromatography were used to determine the obtained product, the gallic acid methyl ester. The product yield was 78%, with a melting point of 203–204 °C and Rf value of 0,75. 1H and 13C NMR were recorded on a JNM-EC Z400R spectrometer (JEOL, Japan) at an operating frequency of 400 MHz for 1H in CD, OD solutions. 1H NMR (400 MHz, DMSO-d6) d 3.79 (3H, s, COOMe), 7.02 (2H, dd, J1=1.88, J2=0.96, Ar-N=2.6). 13C NMR (DMSO-d6): 167.69, 145.16, 138.40, 120.15, 108.72, 50.94, 48.10, 47.96, 47.82, 47.68, 47.53, 47.39, 47.25. IR spectra were recorded on an FT-IR/NIR Spectrum 3 spectrometer (Perkin Elmer, Switzerland) using an ATR system KBr, cm^{-1}, 3514, 3344 cm^{-1} (–OH), 3344, 1468, 1534,1045, 1098, 765, 749 sm^{-1} (Ar-CH), 1468, 1440 sm^{-1} ($-CH_3$), 1686,1612 sm^{-1} (C=O), 1686, 1612 sm^{-1} (COOR).

Synthesis of methyl ester of syringic acid (**2**). Melting point of methyl ester of syringic acid 168–1690 °C, yield 1.68 g (84%), Rf = 0.4. 1H and 13C NMR were recorded on a JNM-EC Z400R spectrometer (JEOL, Japan) at an operating frequency of 400 MHz for 1H in CD, OD solutions. ^{1}H NMR (400 MHz, DMSO-d6) δ 3.84 (3H, c, COOMe), 3.85 (6H, c, OMe-3,5), 7.27 (2H, d, J=1.01, Ar-H=2,6). 13C NMR (DMSO-d6): 167.32, 147.32, 140.84, 119.83, 106.76, 55.45, 51.15, 48.10,

47.96, 47.68, 47.26. IR spectra were recorded on an FT-IR/NIR Spectrum 3 spectrometer (Perkin Elmer, Switzerland) using an ATR system KBr, cm^{-1}, 3554 cm^{-1} (–OH), 2846 sm^{-1} (Ar-OCH_3), 3005, 2950, 1632, 1613, 1107, 1041, 902 sm^{-1} (Ar-CH), 2846, 1446, 1333sm^{-1} (–CH_3), 1682, 1613 sm^{-1} (C=O), 1682, 1613 sm^{-1} (COOR).

Synthesis of methyl ester of 3,4,5-trimethoxybenzoic acid (**3**). Melting point of methyl ester of 3,4,5-trimethoxybenzoic acid is 168–169 º C, yield is 1.78 g (89%), Rf value is 0.5. 1H and 13C NMR were recorded on a JNM-EC Z400R spectrometer (JEOL, Japan) at an operating frequency of 400 MHz for 1H in CD, OD solutions.

1H NMR (400 MHz, DMSO-d6) δ 4.07 (3H, c, COOMe), 4.03 (6H, c, OMe-3,5), 3.78 (3H, c, OMe-4). IR spectra were recorded on an FT-IR/NIR Spectrum 3 spectrometer (Perkin Elmer, Switzerland) using an ATR system KBr, cm^{-1}, 2840 sm^{-1}(Ar-OCH_3), 3015, 1712, 1589, 1507, 1454 sm^{-1} (Ar-CH), 2965 sm^{-1} (–CH_3), 1618sm^{-1} (C=O), 1682, 1622 sm^{-1} (COOR).

Conclusion

Esters were produced by reacting gallic acid, syringic acid, and 3,4,5-trimethoxybenzoic acid with methyl alcohol under the catalysis of sulfuric acid.

The effect of solvent and time on the reaction yield was investigated and the optimum conditions were found. Methods of purification of the obtained substances were determined. The structure of the substances was confirmed by IR and PMR sectors.

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submitted 16.08.2024;
accepted for publication 31.08.2024;
published 28.09.2024

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