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STUDY OF SYNTHESIS OF ETHYL-2-(4-ALLYL-2-METHOXYPHENOXY)ACETATE IN POLAR APROTIC SOLVENTS

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Abstract

Eugenol, a phenol-derived aromatic allylbenzene compound, exhibits a wide spectrum of biological activities (antifungal, antibacterial, antioxidant, analgesic, and antiseptic) and is an active ingredient in various hygiene products. It contains three reactive groups (hydroxy, allyl, and methoxy) and undergoes several reactions, including alkylation. The modification of the hydroxyl group of eugenol through alkylation has been performed using different alkylating agents. Alkylation has been carried out in various solvents (benzene, acetonitrile, methanol, and water) and at diverse temperatures. Hence, the investigation of this alkylation reaction on eugenol remains challenging. Correspondingly, the present study investigated the alkylation of eugenol by ethyl chloroacetate in polar aprotic solvents (N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile, and tetrahydrofuran) at temperatures ranging from 0°C to room temperature. The product, ethyl 2-(4-allyl-2-methoxyphenoxy)acetate (3), was obtained in yields of 91%, 51%, and 47% using DMF, DMSO, and CH3CN, respectively. The product's structure was confirmed by NMR, IR spectroscopy, and HRESIMS analysis.

Keywords: *eugenol; alkylation; aprotic solvents*

Introduction

Eugenol (4-allyl-2-methoxyphenol or 1-allyl-4-hydroxy-3-methoxybenzene), included in the group of phenol-derived aromatic allylbenzene compounds, is the main constituent of the essential oil of clove (*Syzygium aromaticum*) (Marchese et al., 2017; Suryanti et al., 2016). It can also be found in cinnamon, tulsi, and pepper (Khalil et al., 2017). Eugenol exhibits potential as an antifungal, antibacterial, antioxidant, analgesic, and antiseptic agent (Frohlich et al., 2019; Mekky et al., 2023). It has been reported to be active against *Candida albicans*, *Aspergillus niger*, *Saccharomyces cerevisiae*, *Bacillus subtilis*, *Pityrosporum ovale*, *Penicillium chrysogenum*, and *Streptococcus aureus* (Olea et al., 2019; Pinto et al., 2019). Additionally, eugenol has been used as an active ingredient in antiseptics (Wael et al., 2018), aromatherapy, fragrances for perfumes, cosmetics, and detergents (Bendre et al., 2016).

Eugenol, containing hydroxy, allyl, and methoxy groups, is a reactive allylphenol-type phenylpropanoid compound (Ulanowska & Olas, 2021). It undergoes several reactions, including acetylation, esterification, isomerization, alkylation, and addition, which are directly useful or serve as starting points for other compounds (Firdaus et al., 2020; Mishra et al., 2013).

The hydroxyl group of eugenol can be modified to produce ether through Williamson etherification (Suryanto & Anwar, 2012). This hydroxyl group can also undergo alkylation reactions with alkylating agents such as acetyl, propanil, 3-chloropropanil, 3-hydroxypropanil, methyl butanoate, and butanoic acid (Fernandes et al., 2020; Olea et al., 2019). For example, alkylation of eugenol with iodomethane or iodoethane at a temperature of 40–50°C with potassium hydroxide in benzene forms the corresponding ethers, namely 3,4-dimethoxyallylbenzene and 3-methoxy-4-ethoxyallylbenzene (Mikhailovskii et al., 2012). Similarly, alkylation of the hydroxyl group of eugenol has been carried out with 1-bromopropane, 1-bromo-3-chloropropane, 3-bromopropan-1-ol, and ethyl 4-bromobutanoate using cesium carbonate in acetonitrile at 65°C. The alkylation products—4-allyl-2-methoxy-1-propoxybenzene, 4-allyl-1-(3-chloropropoxy)-2-methoxybenzene, 3-(4-allyl-2-methoxyphenoxy)propan-1-ol, and ethyl 4-(4-allyl-2-methoxyphenoxy)butanoate—were obtained in 53–89% yield (Fernandes et al., 2020). Alkylation of eugenol with propargyl bromide was successfully performed using sodium hydroxide in methanol, yielding 4-allyl-2-methoxy-1-(prop-2-yn-1-yloxy)benzene with an 87% yield. The reaction was conducted at 40°C, followed by stirring at room temperature for 18 hours (Oliveira et al., 2019). Methylation of eugenol was also executed with dimethyl carbonate using aqueous sodium hydroxide and a 20% bentonite catalyst. This reaction, performed at a temperature of 120–160°C, afforded methyl eugenol in a 26% yield (Asnawati et al., 2015). Alkylation of eugenol can be accomplished in various solvents, such as benzene, acetonitrile, methanol, and water, at temperatures ranging from 40–65°C to 120–160°C. These findings extend possibilities for investigating the alkylation of eugenol in other solvents and at lower reaction temperatures. Based on the above explanation, this study aimed to investigate the alkylation reaction of eugenol with ethyl chloroacetate in polar aprotic solvents (N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile, and tetrahydrofuran) at temperatures ranging from 0°C to room temperature to produce ethyl 2-(4-allyl-2-methoxyphenoxy)acetate.

Methodology

General Procedure

All chemicals were procured from commercial suppliers (Sigma-Aldrich, Merck, RCI Labscan, Smart-Lab, JT Baker, Fulltime, and VWR Chemical) and used as received. Reaction progress was monitored by thin-layer chromatography (TLC) on silica gel 60 F254 (Merck, Germany). The NMR, IR spectra, and LC-HRMS were used to characterize the synthesized compounds. The IR spectra were recorded on an FT-IR 8400S spectrometer (Shimadzu, Japan). The NMR spectra were recorded on a Bruker Avance Neo NMR 500 MHz spectrometer (Bruker, Switzerland). The LC-HRMS analysis was performed on a Xevo G2-XS QTOF (Waters, USA).

Synthesis of Ethyl 2-(4-allyl-2-methoxyphenoxy)acetate (3)

Eugenol (1) (2.3 mL, 15 mmol) in aprotic solvents (N,N-dimethylformamide, dimethyl sulfoxide, acetonitrile, and tetrahydrofuran) (62.5 mL) was stirred at 0°C (ice bath) for 15 minutes. Potassium carbonate (7.26 g, 52.5 mmol) was added, and the mixture was further stirred at 0°C for 30 minutes. Next, ethyl chloroacetate (2) (6.4 mL, 60 mmol) was added, and the reaction mixture was stirred at 0°C for 1 hour, followed by stirring at room temperature for 3 hours. After the starting material was completely consumed, as indicated by TLC monitoring, the mixture was extracted using dichloromethane (3 × 15 mL) and water (20 mL). The organic phase was combined and dried over Na_2SO_4. The solvents were evaporated under reduced pressure, and the resulting residue was purified by silica gel column chromatography (0.063–0.0200 mm) using a mixture of n-hexane and ethyl acetate. This process afforded ethyl 2-(4-allyl-2-methoxyphenoxy)acetate (3) as a yellow to brownish-yellow oil (DMF: 3.41 g, 91%; DMSO: 1.91 g, 51%; CH_3CN: 1.76 g, 47%

yield); IR (KBr): ν 3077, 2978, 2839, 1759, 1680, 1036 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ 6.81 (d, J = 2 Hz, 1H, CH Ar), 6.78 (d, J = 8 Hz, 1H, CH Ar), 6.66-6.64 (m, 1H, CH Ar), 5.97-5.84 (m, 1H, CH), 5.08-5.02 (m, 2H, CH_2), 4.69 (s, 2H, CH_2), 4.15 (q, J = 7, 7 Hz, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.29 (d, J = 7 Hz, 2H, CH_2), 1.21 (t, J = 7 Hz, 3H, CH_3); HRESIMS [Found: m/z 273.1109 $(M+H)^+$), calcd for $C_{14}H_{18}O_4Na$: $(M+H)^+$, 273.1103].

Results and Discussion

In the present study, the formation of ethyl 2-(4-allyl-2-methoxyphenoxy)acetate (3) from the reaction of eugenol (1) and ethyl chloroacetate (2) followed the scheme displayed in Figure 1. The reaction was conducted in various aprotic solvents, namely N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile (CH_3CN), and tetrahydrofuran (THF), in the presence of potassium carbonate as a base. The reaction proceeded via bimolecular nucleophilic substitution (S_N2), yielding ethyl 2-(4-allyl-2-methoxyphenoxy)acetate (3) in varying percentages depending on the solvent used.

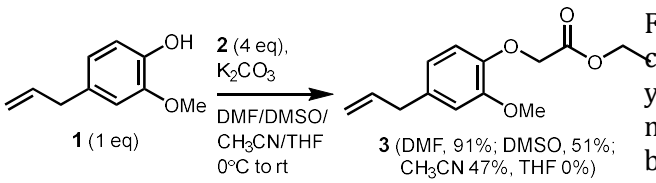

Figure 1. Synthetic scheme of ethyl 2-(4-allyl-2-methoxyphenoxy)acetate (3).

In general, the experiments were carried out by dissolving eugenol (1) in the respective solvent under stirring at 0°C (ice bath), followed by the addition of potassium carbonate (K_2CO_3). Ethyl chloroacetate (2) was then added, and the reaction mixture was stirred further at 0°C and subsequently at room temperature. The progress of the reaction was monitored using thin-layer chromatography (TLC) with n-hexane:ethyl acetate (5:1) as the mobile phase. The TLC profiles obtained with the four solvents at room temperature (see Figure 2) showed the appearance of a new spot with an Rf value distinct from that of eugenol (1). However, the reaction in THF did not progress, prompting termination and further processing of the reaction mixture.

The reaction products were poured onto crushed ice, allowed to reach room temperature, and then extracted with dichloromethane (DCM). The resulting organic phase was washed with distilled water, dried over anhydrous sodium sulfate (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue obtained was purified by column chromatography using n-hexane:ethyl acetate mixtures as the eluent. Fractions with similar Rf profiles were combined, and the solvent was evaporated, yielding ethyl 2-(4-allyl-2-methoxyphenoxy)acetate (3) as a yellow to brownish-yellow oil. A purity test of the product using TLC (see Figure 3) revealed a single spot, indicating that compound (3) was pure.

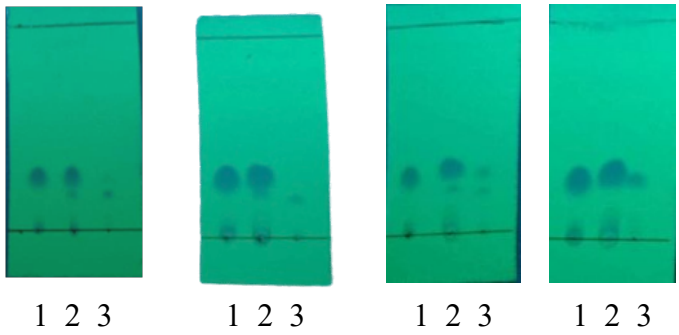

Figure 2. TLC monitoring profile for the synthesis of ethyl 2-(4-allyl-2-methoxyphenoxy)acetate (3) at room temperature in different solvents: DMF (left), DMSO (left-center), CH_3CN (right-center), and THF (right). Key: 1 = eugenol (1), 2 = mix (eugenol (1) + reaction mixture), 3 = reaction mixture.

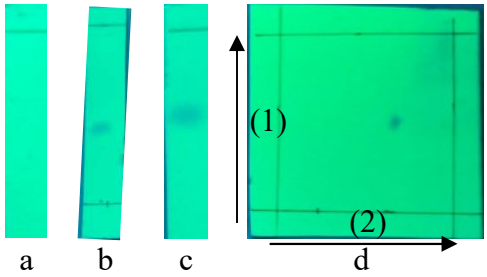

Figure 3. TLC profile of ethyl 2-(4-allyl-2-methoxyphenoxy)acetate (3) in different solvent systems: (a) n-hexane, (b) n-hexane:ethyl acetate (1:1), (c) n-hexane:ethyl acetate (5:1), (d1) n-hexane:ethyl acetate (5:1), (d2) n-hexane:ethyl acetate (1:1).

The synthesis of ethyl 2-(4-allyl-2-methoxyphenoxy)acetate (3) in different polar aprotic solvents from eugenol (1) and ethyl chloroacetate (2) in the presence of K_2CO_3 as the base was carried out. The solvents affected the reaction profile, as indicated by TLC (see Figure 3). The reaction of eugenol (1) and ethyl chloroacetate (2) in DMF, DMSO, and CH_3CN produced ethyl 2-(4-allyl-2-methoxyphenoxy)acetate (3) as an oily product, with a mass and yield of 3.41 g (91%), 1.91 g (51%), and 1.76 g (47%), respectively (see Table 1).

It was noted that eugenol (1) had a large dipole moment related to its molecular polarity, enabling it to form strong nonspecific dipole-dipole interactions with the solvent (Muliadi et al., 2023). The solubility of eugenol (1) was greater in DMF compared to other solvents due to the formation of a hydrogen bond between the -OH group of eugenol (1) and the nitrogen atom of DMF (Solomons et al., 2014). Meanwhile, eugenol (1) was only slightly soluble in DMSO and CH_3CN, affecting the yield of the product (3). THF, a polar aprotic solvent with a small dipole moment and a dielectric constant of less than 10, resulted in the limited solubility of eugenol (1). This condition decreased the nucleophilicity of the reactant, thereby inhibiting the SN2 reaction (Yulianti et al., 2012).

The structure of ethyl 2-(4-allyl-2-methoxyphenoxy)acetate (3) was identified using NMR, IR spectra, and HRESIMS analysis. The ^{1}H NMR spectrum of compound (3) in DMSO-d_6 (500 MHz) (see Figure 5) displayed triplet and singlet signals at δ 1.20 ppm (J = 7 Hz) and δ 3.73 ppm, attributed to CH_3 protons. A singlet at δ 4.67 ppm, a doublet at δ 3.28 ppm (J = 7 Hz), a quartet at δ 4.14 ppm (J = 7, 7 Hz), and a multiplet at δ 5.08–5.02 ppm corresponded to CH_2 protons. The CH proton appeared as a multiplet at δ 5.97–5.84 ppm. The presence of aromatic protons was noted from doublet, doublet, and multiplet signals at δ 6.78 ppm (J = 8 Hz), δ 6.81 ppm (J = 2 Hz), and δ 6.66–6.64 ppm, respectively.

The structural identification of ethyl 2-(4-allyl-2-methoxyphenoxy)acetate (3) by infrared spectroscopy indicated the existence of CH sp^2, CH sp^3, C=O, C=C, and C-O bonds, observed as absorption bands at ν 3077, 2978, 2839, 1759, 1680, and 1036 cm^{-1} (see Figure 6). The molecular mass of ethyl 2-(4-allyl-2-methoxyphenoxy)acetate (3) (see Figure 7) exhibited a molecular ion ($[M+H]^+$) peak at m/z 273.1109 for $C_{14}H_{18}O_4Na$, consistent with the theoretical m/z $[M+H]^+$ 273.1103.

A plausible mechanism for the formation of ethyl 2-(4-allyl-2-methoxyphenoxy)acetate (3) via an S_N2 reaction involved the deprotonation of the hydroxy group of eugenol (1) by the carbonate ion, forming the alkoxide as a nucleophile. A subsequent concerted attack of this species on ethyl chloroacetate (2) led to the formation of product (3).

Table 1. %Yield of ethyl 2-(4-allyl-2-methoxyphenoxy)acetate (3)

Product 3	Solvents			
	DMF	**DMSO**	**CH_3CN**	**THF**
%Yield	91	51	47	0
Appearance	Oily	Oily	Oily	Oily
Color	Yellow	Yellow	Brownish yellow	Blackish

Conclusion

In conclusion, ethyl 2-(4-allyl-2-methoxyphenoxy)acetate (3) was obtained in yields of 91%, 51%, and 47% using DMF, DMSO, and CH_3CN, respectively, as solvents in the reaction between eugenol (1) and ethyl chloroacetate (2). The structure of ethyl 2-(4-allyl-2-methoxyphenoxy)acetate (3) was established through NMR, IR spectroscopy, and HRESIMS analysis.

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References

Asnawati, D., Sudarma, I. M., Yuanita, E., Arlina, B. F., Hamdiani, S. & Kamali, S. R. (2015). Methylation of Eugenolusing Dimethyl Carbonate and Bentonite as Catalyst. *Indonesian Journal of Chemistry*, *15*, 256- 262.

Bendre, R.S., Rajput, J. D., Bagul, S. D. & Karandikar, P. S. (2016). Outlooks on Medicinal Properties of Eugenol and its Synthetic Derivatives. *Natural Products Chemical Research*, *4*, doi:10.4172/2329-6836.1000212

Fernandes, M. J. G., Pereira, R. B., Pereira, D. M., Fortes, A. G., Castanheira, E. M. S. & Gonçalves, M. S. T. (2020). NewEugenol Derivatives with Enhanced Insecticidal Activity. *International Journal of Molecular Sciences*, *21*, 9257.

Firdaus, M., Kusumaningsih, T., Wibowo, A. H. & Hertiningtyas, C. (2020). Green Synthesis of Renewable Dimethyl Terephthalate-like Monomer from Eugenol. *Sains Malaysiana*, *49*, 2715–2720. https://doi.org/10.17576/jsm-2020-4911-10

Frohlich, P. C., Santos, K. A., Palu, F., Cardozo-Filho, L., Silva, C. & Silva, E. A. (2019). Evaluation of The Effects of Temperature and Pressure on The Extraction of Eugenol from Clove (*Syzygium aromaticum*) Leaves Using Supercritical CO_2. *The Journal of Supercritical Fluids*, *143*, 313-320. doi: 10.1016/J.SUPFLU.2018.09.009

Khalil, A. A., Rahman, U. U., Khan, M. R., Sahar, A., Mehmood, T. & Khan, M. (2017). Essential Oil Eugenol: Sources, Extraction Techniques and Nutraceutical Perspectives. *RSC Advances, 7*, 3669-33681. doi:10.1039/c7ra04803c

Marchese, A., Barbieri, R., Coppo, E., Orhan, I. E., Daglia, M., Nabavi, S. F., Izadi, M., Abdollahi, M., Nabavi, S. M. & Ajami, M. (2017). Antimicrobial Activity of Eugenol and Essential Oils Containing Eugenol: A Mechanistic Viewpoint. *Critical Review in Microbiology*, *2017*. doi: 10.1080/1040841X.2017.1295225

Mekky, A. E., Emam, A. E., Selim, M. N., Abdelmouty, E. S. & Khedr, M. (2023). Antibacterial and Antineoplastic MCF-7 and HePG-2 Characteristics of The Methanolic (80%) Clove (*Syzygium aromaticum* L.) Extract. *Biomass Conversion and Biorefinery*.

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https://doi.org/10.1007/s13399-023-03862-1

Mikhailovskii, A. G., Surikova, O. V., Limanskii, E. S. & Vakhrin, M. I. (2012). Synthesis of Isoquinoline Alkaloid Derivatives from Eugenol. *Chemistry of Natural Compounds*, *48*, 285-287.

Mishra, S., Sachan, A. & Sachan, S. G. (2013). Production of Natural Value-added Compounds: An Insight into The Eugenol Biotransformation Pathway. *Journal of The Indian Microbiology Biotechnology*, *40*, 545–550. doi:10.1007/s10295-013-155-9

Muliadi, Setiawan, T., Setiani, I. D., Limatahu, N. A. & Liestianty, D. (2023). Computational Chemistry: QSAR of Dental Disease-Causing Streptococcus mutans Using Eugenol Derivative Compounds from Clove Essential Oil. *Techno*, *12*, 39–45. doi: https://doi.org/10.33387/tjp.v12i1.5793

Olea, A. F., Bravo, A., Martínez, R., Thomas, M., Sedan, C., Espinoza, L., Zambrano, E., Carvajal, D., Silva-Moreno, E. & Carrasco, H. (2019). Antifungal Activity of Eugenol Derivatives Against Botrytis cinerea. *Molecules*, *24*. https://doi.org/10.3390/molecules24071239

Oliveira, A. S. D., Gazolla, P. A. R., Oliveira, A. F. C. D. S., Pereira, W. L., Maia, A. F. D. S., Santos, A. G., Silva, I. E. P. D., Mendes, T. A. D. O., Silva, A. M. D., Dias, R. S., Silva, C. C. D., Polêto, M. D., Teixeira, R. R. & Paula, S. O D. (2019). Discovery of Novel West Nile Virus Protease Inhibitor Based on Isobenzonafuranone and Triazolic Derivatives of Eugenol and Indan-1,3-Dione Scaffolds. *PLoS ONE*, *14*, e0223017

Pinto, S. M. L., Rivera, Y., Sandoval, L. V. H., Lizarazo, J. C., Rincón, J. J. & Méndez, L. Y. V. (2019). Semisynthetic Eugenol Derivatives as Antifungal Agents Against Dermatophytes of The Genus Trichophyton. *Journal of Medical Microbiology*, *68*, 1109–1117. doi:10.1099/jmm.0.001019

Solomons, T. W. G., Fryhle, C. B. & Snyder, S. A. (2014). *Organic Chemistry 11th Edition*. John Wiley dan Sons, Inc.

Suryanti, V., Wibowo, F. R., Kusumaningsih, T., Wibowo, A. H., Khumaidah, S. A. & Wijayanti, I. A. (2016). Amidation Reaction of Eugenyl Oxyacetate Ethyl Ester with 1, Diaminopropane. *AIP Conference Proceedings*, *1725*, 020085. doi:10.1063/1.4945539

Suryanto, E. & Anwar, C. (2012). Sintesis Antioksidan 4,6-Dialil-2-Metoksifenol dari Alil Eugenol Melalui Penataan Ulang Claisen. *Chemistry Progress*, *1*, 1–8.

Ulanowska, M. & Olas, B. (2021). Biological Properties and Prospects for The Application of Eugenol-a review. *International Journal of Molecular Sciences*, *22*, 3671. https://doi.org/10.3390/ijms22073671

Wael, S., Mahulette, F., Watuguly, T. W. & Wahyudi, D. (2018). Effect of Leaf Syzygium aromaticum on Lymphocytes and Macrophages Mice Balb/c. *Traditional Medicine Journal*, *23*, 79–83.

Yulianti, R., Onggo, H. & Syampurwadi, A. (2012). Effect of Dielectric Constant And Dispersion of Particle on Hydrophobicity of Carbon Nanotube Based Electrocatalyst Film. *Indonesian Journal of Materials Science*, *14*, 224-28.