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Synthesis and Antibacterial Activity of Isoeugenol Ether Derivatives

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Abstract: Isoeugenol has wide medical applications. It is used in manufacturing perfumeries, flavorings, essential oils and in medicine (local antiseptic and analgesic). Its analogues also show many biological activities which prompted us to synthesize few more analogues for their future application as bioactive molecules. All these analogues were unambiguously characterized by ¹H NMR and Mass spectral data and screened for their potential antibacterial activity against Gram positive and Gram negative cultures. Few of them possess promising antibacterial activity.

I. INTRODUCTION

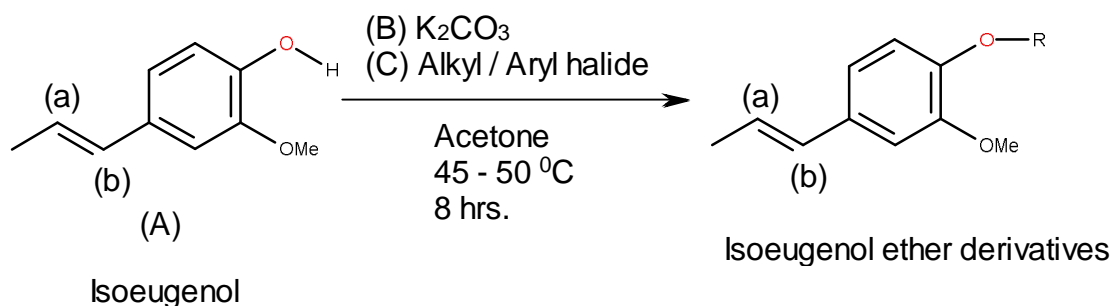
Phenolic compounds exist in most plant tissues as secondary metabolites i.e. they are not essential for growth, development or reproduction but may play roles as antioxidants and in interactions between the plant and its biological environment. Phenolics are also important components of the human diet due to their potential antioxidant activity¹, their capacity to diminish oxidative stress induced tissue damage resulted from chronic diseases², and their potentially important properties such as anticancer activities³⁻⁵. One of such compound is Isoeugenol which is a phenyl propene, a propenyl substituted guaiacol. It occurs in the essential oils of plants such as ylang-ylang. It can be synthesized from eugenol and had been used in the manufacture of vanillin. It may occur as either the cis (Z) or trans (E) isomer. Trans (E) isoeugenol is crystalline while cis (Z) isoeugenol is a liquid⁶. In the present study, we are diversifying isoeugenol to its ether derivatives using conventional method. The objective of this study is to condense two molecules of the same disease domain to produce more potent candidate in the same disease domain or to condense two molecules of different disease domain to produce mixed variety of those disease domain or to have drug candidate with entirely different disease domain.

II. RESULTS AND DISCUSSION

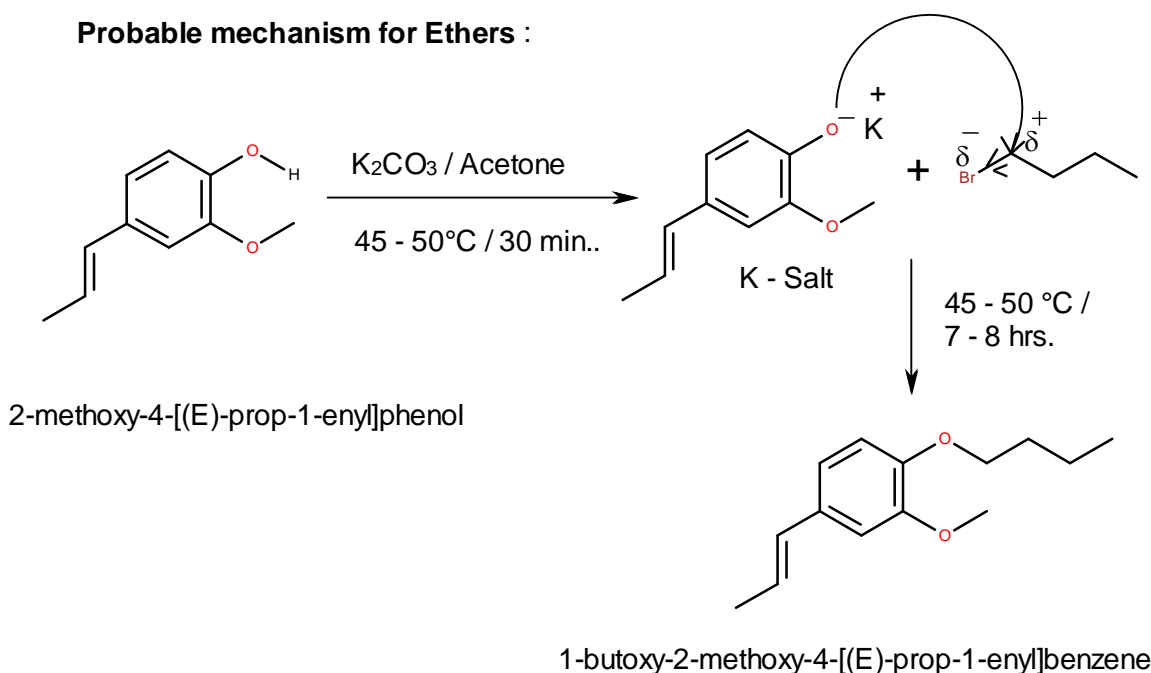
Isoeugenol is treated with potassium carbonate in acetone to form K-salt which in turn reacted with suitable alkyl / aryl halide at ambient temperature for 24 hrs. to yield respective ether derivatives. The crude reaction mixture obtained in each stages were purified by column, radial and preparative thin layer chromatographic techniques and unambiguously characterized by ¹H NMR and Mass spectroscopy techniques. General method for the preparation of compounds (1 - 9) :- These were prepared by following general method as depicted below. To a stirred solution of [A] (1 eq.) in 30 ml acetone was added [B] (2.5 eq.) and stirring continued at 40°C for next 30 min. for complete formation of K-salt. To this compound [C] (2 eq.) was added and stirring continued at 45 – 50°C for next 8 h. The progress of the reaction is monitored by TLC for the completion of the reaction.

Work up :- The reaction mixture filtered through buchner funnel, wash the cake with 25 ml acetone. The total organic layer was concentrated to minimum, preadsorbed on silica gel and purified by silica gel (100 – 200 mesh) column chromatography with increase in concentration of ethyl acetate in petroleum ether. The general yields ranges between 60 – 80 %.

Synthetic Scheme :



| Compound No. | R |
|--------------|-----------|
| 1 | Methyl |
| 2 | Ethyl |
| 3 | n-Propyl |
| 4 | Allyl |
| 5 | n-Butyl |
| 6 | n-Heptyl |
| 7 | n-Dodecyl |
| 8 | Acetone |
| 9 | Benzyl |

Probable mechanism for Ethers :

A. Compound 1 :- 1,2-dimethoxy-4-[(1E)-prop-1-en-1-yl]benzene

¹H NMR (400 MHz, CDCl₃) δppm : 1.84 (d, 3H, J = 7.6 Hz, terminal methyl from isoeugenol moiety), 3.84 (s, 3H, Ar x -OCH₃), 3.86 (s, 3H, Ar x -OCH₃), 6.0 – 6.25 (m, 1H, olefinic proton 'a'), 6.32 (d, J = 15.8 Hz, 1H, olefinic proton 'b'), 6.7 – 7.0 (m, 3H, ArH). TOF MS ES: 179 (M + H). Molecular formula C₁₁H₁₄O₂. Pure viscous mass (0.89 gms, 82 %). Anal. Calcd. for C₁₁H₁₄O₂ : C 74.13, H 7.92, O 17.95 Found C 74.10, H 7.88, O 17.98;

B. Compound 2 :- 1-ethoxy-2-methoxy-4-[(1E)-prop-1-en-1-yl]benzene

¹H NMR (400 MHz, CDCl₃) δppm : 1.45 (t, J = 7.0 Hz, 3H, from -OCH₂CH₃ ethyl bromide moiety), 1.86 (d, 3H, J = 6.7 Hz, terminal methyl from isoeugenol moiety), 3.88 (s, 3H, Ar x -OCH₃), 4.025 (q, J = 6.8 Hz, 14Hz, 2H, from -OCH₂CH₃ ethyl bromide moiety), 6.0 – 6.2 (m, 1H, olefinic proton 'a'), 6.33 (d, J = 15.6 Hz, 1H, olefinic proton 'b'), 6.7 – 7.0 (m, 3H, ArH). TOF MS ES: 193 (M + H). Molecular formula C₁₂H₁₆O₂. Pure viscous mass (0.913 gms, 78 %). Anal. Calcd. for C₁₂H₁₆O₂ : C 74.97, H 8.39, O 16.64 Found C 74.94, H 8.42, O 16.67;

C. Compound 3 :- 2-methoxy-4-[(1E)-prop-1-en-1-yl]-1-propoxybenzene

¹H NMR (400 MHz, CDCl₃) δppm : 1.03 (t, J = 7.3 Hz, 3H, terminal methyl from n-propylbromide moiety), 1.7 – 2.0 (m, 2H, -CH₂ from n-propylbromide moiety), 1.86 (d, J = 8.6 Hz, 3H, terminal methyl from isoeugenol moiety), 3.87 (s, 3H, Ar x -OCH₃), 3.96 (t, J = 7.9 Hz, 2H, -OCH₂ from n-propyl bromide moiety), 6.0 – 6.25 (m, 1H, olefinic proton 'a'), 6.33 (d, J = 15.8 Hz, 1H, olefinic proton 'b'), 6.7 – 7.0 (m, 3H, ArH). TOF MS ES: 207 (M + H). Molecular formula C₁₃H₁₈O₂. Pure viscous mass (1.0 gms, 80 %). Anal. Calcd. for C₁₃H₁₈O₂ : C 75.69, H 8.80, O 15.51 Found C 75.66, H 8.84, O 15.54;

D. Compound 4 :- 2-methoxy-4-[(1E)-prop-1-en-1-yl]-1-(prop-2-en-1-yloxy)benzene

¹H NMR (400 MHz, CDCl₃) δppm : 1.85 (d, J = 7.8 Hz, 3H, terminal methyl from isoeugenol moiety), 3.86 (s, 3H, Ar x -OCH₃), 4.58 (d, J = 7.5 Hz, 2H, -OCH₂ from allyl bromide moiety), 5.32 (dd, J = 15.0 Hz, 2H, =CH₂ from allyl bromide moiety), 5.9 – 6.2 (m, 1H, olefinic proton 'a'), 6.32 (d, J = 15.6 Hz, 1H, olefinic proton 'b'), 6.7 – 7.0 (m, 3H, ArH). TOF MS ES: 205 (M + H). Molecular formula C₁₃H₁₆O₂. Pure viscous mass (0.896 gms, 72 %). Anal. Calcd. for C₁₃H₁₆O₂ : C 76.44, H 7.90, O 15.67 Found C 76.40, H 7.94, O 15.70;

D. Compound 5 :- 1-butoxy-2-methoxy-4-[(1E)-prop-1-en-1-yl]benzene

¹H NMR (400 MHz, CDCl₃) δppm : 0.97 (t, J = 7.9 Hz, 3H, terminal methyl from n-butyl bromide moiety), 1.4 – 1.6 (m, 2H, -CH₂ from n-butyl bromide moiety), 1.7 – 2.0 (m, 2H, -CH₂ from n-butyl bromide moiety), 1.90 (d, J = 7.3 Hz, 3H, terminal methyl from isoeugenol moiety), 3.87 (s, 3H, Ar x -OCH₃), 4.0 (t, J = 7.3 Hz, 2H, -OCH₂ from n-butyl bromide moiety), 6.0 – 6.2 (m, 1H, olefinic proton 'a'), 6.33 (d, J = 15.8 Hz, 1H, olefinic proton 'b'), 6.7 – 7.0 (m, 3H, ArH). TOF MS ES: 221 (M + H). Molecular formula C₁₄H₂₀O₂. Pure viscous mass (1.02 gms, 76 %). Anal. Calcd. for C₁₄H₂₀O₂ : C 76.33, H 9.15; O 14.52. Found C 76.29, H 9.12, O 14.55;

E. Compound 6 :- 1-(heptyloxy)-2-methoxy-4-[(1E)-prop-1-en-1-yl]benzene

¹H NMR (400 MHz, CDCl₃) δppm : 0.88 (t, J = 7.9 Hz, 3H, terminal methyl from n-heptyl bromide moiety), 1.0 – 1.6 (m, 10H, 5 x -CH₂ from n-heptyl bromide moiety), 1.86 (d, J = 8.5 Hz, 3H, terminal methyl from isoeugenol moiety), 3.87 (s, 3H, Ar x -OCH₃), 3.99 (t, J = 7.0 Hz, 2H, -OCH₂ from n-heptyl bromide moiety), 6.0 – 6.2 (m, 1H, olefinic proton 'a'), 6.32 (d, J = 15.6 Hz, 1H, olefinic proton 'b'), 6.6 – 7.0 (m, 3H, ArH). TOF MS ES: 263 (M + H). Molecular formula C₁₇H₂₆O₂. Pure viscous mass (1.018 gms, 74 %). Anal. Calcd. for C₁₇H₂₆O₂ : C 77.82, H 9.99, O 12.20 Found C 77.78, H 9.95, O 12.24;

F. Compound 7 :- 1-dodecyloxy-2-methoxy-4-[(1E)-prop-1-en-1-yl]benzene

¹H NMR (400 MHz, CDCl₃) δppm : 0.83 (t, J = 7.3 Hz, 3H, terminal methyl from n-dodecanyl bromide moiety), 1.0 – 1.6 (m, 18H, 9 x -CH₂ from n-dodecanyl bromide moiety), 1.90 (d, J = 7.3 Hz, 3H, terminal methyl from isoeugenol moiety), 3.87 (s, 3H, Ar x -OCH₃), 4.0 (t, J = 7.3 Hz, 2H, -OCH₂ from dodecanyl bromide moiety), 6.0 – 6.2 (m, 1H, olefinic proton 'a'), 6.32 (d, J = 15.8 Hz, 1H, olefinic proton 'b'), 6.6 – 7.0 (m, 3H, ArH). TOF MS ES: 333 (M + H). Molecular formula C₂₂H₃₆O₂. Pure viscous mass (1.078 gms, 71 %). Anal. Calcd. for C₂₂H₃₆O₂ : C 79.46, H 10.91, O 9.62 Found C 79.42, H 10.88, O 9.66;

G. Compound 8 :- 1-(2-methoxy-4-[(1E)-prop-1-en-1-yl]phenoxy)propan-2-one

¹H NMR (400 MHz, CDCl₃) δppm : 1.84 (d, J = 6.7 Hz, 3H, terminal methyl from isoeugenol moiety), 2.27 (s, 3H, -COCH₃ from monochloro acetone moiety), 3.88 (s, 3H, Ar x -OCH₃), 4.55 (t, J = 7.3 Hz, 2H, -OCH₂ from monochloro acetone moiety), 6.0 – 6.2 (m, 1H, olefinic proton 'a'), 6.34 (d, J = 15.8 Hz, 1H, olefinic proton 'b'), 6.6 – 7.0 (m, 3H, ArH). ¹³C NMR (100 MHz, CDCl₃) δppm : 18.61 (Terminal methyl from isoeugenol moiety), 26.61 (-COCH₃, terminal methyl from monochloro acetone moiety), 55.99 (Ar x -OCH₃), 74.75 (-OCH₂), 109.57 (=CH, olefinic carbon 'a'), 114.34 (=CH, olefinic carbon 'b'), 118.77 (ArC), 124.96 (q, >C<), 130.52 (ArC), 133.02 (ArC), 146.59 (q, ArC-O), 149.77 (q, ArC-O), 206.64 (q, >C=O). TOF MS ES: 221 (M + H). Molecular formula C₁₃H₁₆O₃. Pure viscous mass (0.93 gms, 69 %). Anal. Calcd. for C₁₃H₁₆O₃ : C 70.89, H 7.32, O 21.79 Found C 70.85, H 7.28, O 21.83;

H. Compound 9 :- 1-(benzyloxy)-2-methoxy-4-[(1E)-prop-1-en-1-yl]benzene

¹H NMR (400 MHz, CDCl₃) δppm : 1.84 (d, J = 7.6 Hz, 3H, terminal methyl from isoeugenol moiety), 3.88 (s, 3H, Ar x -OCH₃), 5.13 (s, 2H, Benzylic -CH₂), 6.0 – 6.2 (m, 1H, olefinic proton 'a'), 6.32 (d, J = 15.6 Hz, 1H, olefinic proton 'b'), 6.6 – 7.5 (m, 8H, ArH from isoeugenol and benzyl bromide moiety). TOF MS ES: 255 (M + H). Molecular formula C₁₇H₁₈O₂. Pure viscous mass (1.29 gms, 83 %). Anal. Calcd. for C₁₇H₁₈O₂ : C 80.28, H 7.13, O 12.58 Found C 80.25, H 7.10, O 12.62;

I. Advantages

- 1) Use of simple and inexpensive reactants (NaOH, KOH, K₂CO₃ etc. instead of NaH, KHMDS t-BuOK, etc.)
- 2) High yields and purity of products.
- 3) Simplicity of the procedure.
- 4) Highly scalable.

III. EXPERIMENTAL

Mps. are uncorrected. ¹H and ¹³C NMR spectra were recorded at 400 MHz on a Varian spectrometer and Mass spectra on TOF MS ES mode. Elemental analysis was carried out as a percentage on a Thermo finnigan, Flash EA 1112 series, Italy.

A. Chromatographic system

Column chromatography: For column chromatography 100 – 200 mesh Acme grade silica gel is used. The crude reaction mixture is concentrated under reduced pressure to yield crude mass which is preadsorbed on silica gel and purified by column chromatography with increase in concentration of Ethyl acetate in Petroleum ether. The fractions having similar “rf” values were pooled together, concentrated and subjected for characterization using various spectroscopic techniques.

Thin layer chromatography: TLC plates were prepared using silica gel G (ACME, BOMBAY). Pet. ether: EtOAc (85 : 15) was used as the solvent system.

Radial chromatography: The circular glass plates of thickness 1 mm, were prepared by using silica gel (PF254, E. MERCK, 50 g) in cold distilled water (105 ml). For elution, gradually increasing concentrations of EtOAc in pet ether were employed.

IV. BIOLOGICAL ACTIVITY

Antibacterial Activity using agar diffusion method⁷ :- Conc 100 μm

The synthesized molecules were screened for their antibacterial activity using agar diffusion method at 100 μm concentration against Gram positive (*Staphylococcus aureus*, *Corynebacterium diphtheriae*) and Gram negative (*Escherichia coli*, *Salmonella typhi*, *Klebsiella pneumoniae*) bacterial species qualitatively. The results of the antibacterial activities are summarized in Table 1.

Table 1: Antibacterial Activity Results

| SAMPLE NO. | ACTIVE AGAINST |
|------------|--|
| Isoeugenol | <i>Staphylococcus aureus</i> [Gram positive] <i>Escherichia coli</i> [Gram negative] |
| 4 | <i>Staphylococcus aureus</i> [Gram positive] <i>Escherichia coli</i> [Gram negative] |
| 7 | <i>Staphylococcus aureus</i> [Gram positive] <i>Escherichia coli</i> [Gram negative] |
| 8 | <i>Staphylococcus aureus</i> [Gram positive] <i>Escherichia coli</i> [Gram negative] |
| 9 | <i>Staphylococcus aureus</i> [Gram positive] <i>Corynebacterium diphtheriae</i> [Gram positive] <i>Salmonella typhi</i> [Gram negative] <i>Klebsiella pneumoniae</i> [Gram negative] <i>Escherichia coli</i> [Gram negative] |

The above results show that the base molecule, isoeugenol has antibacterial activity against both the bacterial cultures. Its derivatives viz. 4, 7, 8 and 9 were also active against certain Gram positive and Gram negative cultures respectively. Thus, long chain and aromatic ether derivatives 4, 7, 8 and 9) were potential antibacterial candidates. In depth analysis of these compounds through structure activity relationship studies would provide further insight and can be an interesting topic of future studies.

The structural diversity and the pronounced biological activities encountered in the isoeugenol ether derivatives suggests that this class of compounds is worthy for further studies that may lead to derivatives by using combinatorial chemistry approach is an alternative strategy to new therapeutic discovery. In other words the generation of diverse isoeugenol ether derivatives develops new therapeutic molecules that might result in candidates having better activity.

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