Synthesis and antimicrobial activity of 1-[3-methoxy-4-[4-chlorophenylthioethoxy]-5-iodophenyl]prop-2-ene-1-one and its intermediates

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In recent years 1-[3,4,5-trimethoxyphenyl]prop-2-ene-1-one was used as an intermediate for the synthesis of 2,5-transdiaryltetrahydrofuran (potent PAF antagonist). Some of the examples of PAF antagonist prepared by this intermediate are CMI-392, CMI-206, MK-287, L-652, 753, L-659, 989 etc. We report herein the synthesis and antimicrobial activity of our title compound which is used as an intermediate for the synthesis of 2,5-transdiaryltetrahydrofuran.

Condensation of our title compound with 3,4,5-trimethoxybenzaldehyde following Biftu et al., procedure gave 1,4-diketone. Reduction of diketone with NaBH₄ in CH₃OH (methanol) and tetrahydrofuran gave the 1,4-diol which was cyclised with orthophosphoric acid in benzene at reflux temperature to give an equilibrium mixture of cis and trans isomers of 2,5-transdiaryltetrahydrofuran. Synthesis of 2,5-transdiaryltetrahydrofuran is outlined in Scheme I.

Compound 8 was obtained in three steps from compound 4, following the procedure as previously described. Compound 3 was prepared by alkylation of compound 2 with 1,2-dibromoethane in 50% yield. Reaction of 3 with para-chlorothiophenol gave 4 in 86.2% yield. Synthesis of 8 is outlined in Scheme II.

Measurement of antimicrobial activity

The title compound and its intermediates were dissolved in dimethyl sulfoxide at 200 µg/mL concentration. The composition of nutrient agar medium was 10 g bacto tryptone, 5 g yeast extract, 10 g NaCl, final pH 7.4. After 18 hr the exponentially growing cultures of the four bacteria in nutrient broth at 37°C were diluted in further sterile broth. From each of these diluted cultures, 1 mL was added to 100 mL sterilized and cooled nutrient agar media to give a final bacterial count of 1 × 10⁶ cells/mL. The plates were allowed to set at room temperature and later dried at 37°C for 2 hr. Paper discs (6mm, punched from whatmann no. 41 paper) were ultraviolet sterilised and were used for the assay. Discs were soaked in different concentration of the test solution and placed on the inoculated agar media at regular intervals of 6-7 cm and care was taken to ensure that excess solution was not on the discs. All samples were taken in triplicates. The plates were incubated at 37°C in an inverted fashion.

Antimicrobial activity of title compound and its intermediates

The following bacterial cultures were tested for their susceptibility to title compound 8 and its intermediates by the disc diffusion method in nutrient agar media; Escherichia coli, Proteus vulgaris, Staphylococcus aureus, Bacillus subtilis. The results obtained are shown in Table I.

Compounds 8 is highly active against Staphylococcus aureus and Bacillus subtilis and moderately active against E. coli. Compound 5 is also highly active against Staphylococcus aureus and Bacillus subtilis and moderately active against E. coli and Proteus vulgaris. Compound 4 is moderately active against E. coli and partially active against Bacillus subtilis. Compound 3 is moderately active E. coli, proteus vulgar, Staphylococcus aureus. Compound 2 has no activity against any of the bacteria mentioned above.

General methods

Purify of the synthesized compounds and the progress of the reactions were monitored by TLC.
Reagents: a) Triethylamine, DMF, Thiazolium catalyst Δ; b) NaBH₄ tetrahydrofuran, CH₃OH; c) Orthophosphoric acid, Benzene, reflux.

Scheme I

Reagents: a) I₂, NaOH, H₂O, Δ; b) K₂CO₃, 1,2-dibromoethane, DMF, Δ; c) para-chlorothiophenol, NaOMe, tetrahydrofuran; d) para-formaldehyde (HCHO), N,N-dimethylammonium hydrochloride, Isopropyl alcohol (IPA), reflux; e) Ethylacetate, NaOH; f) Methyl iodide (CH₃I), ethyl acetate; g) H₂O, ethylacetate.

Scheme II

using silica gel GF coated plates. The spots were detected by placing the developed plates in an UV cabinet. All melting points were determined in an open glass capillaries. ¹H NMR were recorded on a Varian XL200 pulsed Fourier transform instrument. Unless specified, NMR spectra were recorded at ambient temperature in CDCl₃ and chemical shifts (δ) are reported relative to TMS as an internal standard. Routine column chromatography was inducted using silica gel 60-120 mesh.
Experimental Section

Ethanone-1-(3-methoxy-4-hydroxy-5-iodophenyl) 2. To the stirred solution of 225 mL of water containing NaOH (7.2 g, 0.18 moles) was added 1 (25 g, 0.15 moles) and heated to 78°C. To the above reaction contents, iodine (38.8 g, 0.15 moles) was added in three portions and refluxed for 3.5 hr. Cool the reaction contents and then filtered the yellow crystalline solid (30.74 g, 75%), m.p. 86.2 °C, m.p. 89 °C.

Ethanone-1-(3-methoxy-4-bromoethoxy-5-iodophenyl) 3. To a stirred solution of K$_3$CO$_3$ (14.17 g, 102 mmole) in dimethyl formamide (125 mL) was added dropwise a solution of 2 (25 g, 85 mmole) in DMF (50 mL) at room temperature. The reaction mixture was stirred for 30 min. and then 1,2-dibromoethane (24.57 ml, 275 mmole) was added dropwise. After the addition, the reaction mixture was stirred at 78°C for 3.5 hr. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and saturated NaCl, dried over MgSO$_4$, filtered, and evaporated in vacuo to yield 3 as solid material (17.0 g, 50%), m.p. 78-80°C which was used without further purification.

$^1$H NMR : δ 4.20 (s, 3H), 3.68 (t, 2H), 3.90 (s, 3H), 4.35 (t, 2H, $J = 10$ Hz), 7.5 (s, 1H), 7.9 (s, 1H).

Ethanone-1-[3-methoxy-4-(4-chlorophenylthioethoxy)-5-iodophenyl] 4. To a stirred solution of 3 (15 g, 37 mmole) in THF (75 mL) was added 4-chlorothiophenol (5.97 g, 41 mmole) and NaOMe (2.45 g, 45 mmole). The reaction mixture was stirred at room temperature for 8 hr and then solvent was removed. The residue was purified by flash column chromatography (silicagel, 3:1 hexane/ethyl acetate) to yield a pale yellow crystalline solid (15.0 g, 86.2%), m.p. 98°C.

$^1$H NMR : δ 7.31 (m, 4H), 7.41 (s, 1H), 7.90 (s, 1H).

Table I—Antimicrobial activity

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<th>4</th>
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<td>-</td>
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<tr>
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</table>

Symbols: ++ = highly active; + = moderately active; - = inactive; ± = partially active

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References