Substituted benzaldehydes and its derivatives are of increasing importance in the organic synthesis, as they can be easily converted to 2,5-diaryl tetrahydrofurans, when condensed with either 1-[3,4,5-trimethoxy phenyl] prop-2-ene-1-one or substituted prop-2-ene-1-phenyl derivatives. But 1-[3,4,5-trimethoxy phenyl] prop-2-ene-1-one is the essential requirement for the synthesis of L-652, 753, L-659, 989MK-287, CMI-206, CMI-392 etc. (examples of trans-2,5-diaryl tetrahydrofurans).

In recent years, some of the 2,5-diaryl tetrahydrofuran derivatives, have been identified to associate to various biological activities and pathways making it one of the important mediators responsible for variety of physiological processes including activation or coagulation of platelets, pathogenesis of immune complex deposition, asthma, ischemia, toxic shock etc. We report herein the synthesis and antimicrobial activities of our title compound and its intermediates, which is used as an important intermediate for the synthesis of 2,5-trans-diaryl tetrahydrofurans.

Condensation of our title compound with 1-[3,4,5-trimethoxy phenyl] prop-2-ene-1-one following Biflu et al., procedure\(^3\) gave 1,4 diketone. Reduction of diketone with NaBH\(_4\) in methanol and tetrahydrofuran gave the 1,4-diol which was cyclised with ortho phosphoric acid in benzene at reflux temperature to give an equilibrium mixture of \(e\text{is}\) and \(t\text{rans}\) isomers of 2,5-diaryl tetrahydrofuran. Synthesis of 2,5 diaryl tetrahydrofuran is outlined in Scheme I.

Iodination of vanillin 1 yielded 5-iodo-vanillin 2 in 75% yield. Compound 3 was prepared by alkylation of 5-iodovanillin with 1,2-dibromo ethane in 45% yield. Compounds 4 and 5 were prepared by alkylation of compound 3 with \(p\)-chlorothiophenol and \(p\)-fluorothiophenol respectively. Reaction of compound 4 and 5 with CuCN in DMF gave compounds 6 and 7 (79% yield). Synthesis of 6 and 7 is outlined in the Scheme II.

Measurement of antimicrobial activity

The title compound and its intermediates were dissolved in dimethyl sulphoxide at 200 \(\mu\)g/mL concentration. The composition of nutrient agar medium was 10 g Bactotryptone, 5 g yeast extract, 10 g NaCl, final pH 7.4. After 18 h the exponentially growing cultures of the six 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 \(1 \times 10^6\) cells/mL. The plates were allowed to set at room temperature and later dried at 37°C for 2 hr. Paper discs (6 mm, 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, 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 6 and its intermediates by the disc diffusion method in nutrient agar media. Gram positive : \(\text{Streptococcus pyogenes}\) and \(\text{Staphylococcus aureus}\). Gram negative : \(\text{Escherichia coli}\) and \(\text{Shigella sonnei}\).
coli, Pseudomonas arzenosa, Proteus vulgaris, salmonella typhii. The results obtained are shown in Table I.

Title compound 6 is moderately active against Streptococcus pyogenes and Escherichia coli, whereas compound 7 (p-fluoro substituent) is moderately active against Escherichia coli and Salmonella typhii. Vanillin (1) is highly active against Pseudomonas arzenosa and moderately active against Staphylococcus aureus, and Escherichia coli whereas its iodinated product 2 is moderately active against Streptococcus pyogenes and Escherichia coli. Compound 3 is highly active against Streptococcus pyogenes and moderately active against Escherichia coli and Salmonella typhii. Compound 4 is highly active against Escherichia coli and inactive against other bacterial cultures (mentioned above).

Compound 5 is highly active against Streptococcus pyogenes and Pseudomonas arzenosa and moderately active against Staphylococcus aureus, Escherichia coli, Proteus vulgaris.

General Methods
Purity of the synthesized compounds and the progress of the reactions were monitored by TLC using silicagel GF 25U coated plates. The spots were detected by placing the developed plates in an U.V cabinet. All melting points were determined in an
open glass capillaries. $^1$H NMR were recorded on a varian XL 200 pulsed fourier transform instrument unless specified. NMR spectra were recorded at ambient temperature in CDCl$_3$ and chemical shifts ($\delta$) are reported relative to TMS as an internal standard. Routine column chromatography was inducted using silica gel 60-120 mesh.

**Experimental Section**

3-Methoxy-4-hydroxy-5-iodo benzaldehyde 2. To the stirred solution of NaOH (7.2 g, 0.18 mole) in water (2.25 mL) was added compound 1 (23 g, 0.15 mole) and heated to 88°C. To the above reaction mixture, iodine (38.8 g, 0.15 mole) was added in three portions and the mixture refluxed for 3.5 hr. The reaction mixture was cooled and then filtered to give the yellow crystalline solid (31.54 g, 75%), m.p. 182-83°C (lit. m.p. 183-85°C); $^1$H NMR (CDCl$_3$) : $\delta$ 3.98 (s, 3H), 7.34 (s, 1H), 7.81 (s, 1H), 9.73 (s, 1H), 10.04 (s, 1H); $^{13}$C NMR (CDCl$_3$) : $\delta$ 55.84, 82.45, 109.34, 129.67, 134.93, 146.85, 152.12, 188.92; IR : 3186, 2847, 1666, 1459, 1259, 854, 670 cm$^{-1}$; Mass (70 ev) : 278 (M$^+$), 263, 235, 135, 79, 51.

3-Methoxy-4-bromoethoxy-5-iodo benzaldehyde 3. To a solution of compound 2 (25 g, 0.875 mole) in DMF (500 mL) was added potassium carbonate (14.89 g, 0.107 mole). The mixture was heated to 80°C to get a clear solution. 1,2-Dibromoethane (54.72 g, 0.28 mole) was added and the reaction...
mixture was then stirred at 80°C for 4 hr. The reaction mixture was diluted with water (250 mL) and extracted with ethyl acetate (125 mL). The organic layer was washed with water (150 mL) and brine (150 mL), dried over MgSO₄, filtered and evaporated to give the title compound as a yellow solid (15.52 g, 45%). m.p.: 73-75°C; ¹H NMR (CDCl₃): δ 3.70 (t, 2H, J = 6.0 Hz), 3.90 (s, 3H), 4.40 (t, 2H, J = 6.0 Hz), 7.41 (s, 1H), 7.82 (s, 1H); ¹³C NMR (CDCl₃): δ 29.96, 56.09, 72.49, 92.15, 111.16, 133.15, 134.40, 152.54, 189.50; IR: 3448, 2965, 1672, 1476, 1427, 1280, 1160, 1034 cm⁻¹; Mass (70 ev): 384 (M⁺) 305, 277, 221, 178, 150, 122, 107, 79, 51; HRMS: m/z Calcd for C₁₀H₁₀O₃Br: 384.6233; Found: 384.6248.

3-Methoxy-4-(4-chlorophenyl thioethoxy)-5-iodobenzaldehyde 4. To a stirred solution of compound 3 (25 g, 0.065 mole) in THF (125 mL) was added 4-chlorothiophenol (10.25 g, 0.071 mole) and sodium methoxide (4.25 g, 0.078 mole) at 5-10°C. The reaction mixture was stirred at room temperature for 8 hr and then solvent was removed. The residue was purified by flash column chromatography (hexane: ethyl acetate: 3:1) to yield a pale yellow solid (25.63 g, 88%). m.p.: 64-65°C; ¹H NMR (CDCl₃): δ 3.35 (t, 2H, J = 6.2 Hz), 7.31 (m, 4H), 7.38 (s, 1H), 7.84 (s, 1H), 9.82 (s, 1H); ¹³C NMR (CDCl₃): δ 33.45, 55.95, 71.14, 92.41, 110.97, 128.59 (3C), 130.77 (3C), 133.90, 134.45 (2C), 152.53, 189.35; IR: 3447, 2831, 1695, 1451, 1382, 1266, 1136, 1038, 976, 814, 660 cm⁻¹; Mass (70 ev): 447 (M⁺) 305, 277, 221, 178, 150, 122, 107, 79, 51; HRMS: m/z Calcd for C₁₀H₁₀O₃Br: 384.6233; Found: 384.6248.

3-Methoxy-4-(4-fluorophenylthioethoxy)-5-cyanobenzaldehyde 5. A mixture of 4 (25 g, 0.056 mole) and CuCN (62 g, 0.069 mole) in DMF (125 mL) was heated with stirring at 15°C for 5 hr. The reaction mixture was cooled, diluted with water (75 mL) and extracted with ethyl acetate (125 mL). The extract was washed with water and saturated NaCl solution, dried over MgSO₄, filtered and evaporated. The title compound was purified by flash column chromatography to yield yellow solid (15.33 g, 79%). m.p.: 89-91°C; ¹H NMR (CDCl₃): δ 3.31 (t, 2H, J = 6.2 Hz), 3.88 (s, 3H), 4.41 (t, 2H, J = 6.2 Hz), 7.27 (m, 4H), 7.73 (s, 1H), 7.86 (s, 1H), 9.78 (s, 1H); ¹³C NMR (CDCl₃): δ 33.55, 56.09, 72.03, 114.46, 127.92, 128.94 (3C), 130.77 (3C), 131.10, 134.45 (3C), 132.37, 132.43, 154.54, 154.59; IR: 3448, 2223, 1700, 1477, 1382, 1293, 1096, 1071, 964, 808, 635 cm⁻¹; Mass (70 ev): 347 (M⁺), 177, 171, 143, 108, 73, 45; HRMS: m/z Calcd for C₁₇H₁₆O₃SNCl: 347.8011; Found: 347.8016.

3-Methoxy-4-(4-fluorophenylthioethoxy)-5-cyanobenzaldehyde 7. ¹H NMR (CDCl₃): δ 3.30 (t, 2H, J = 6.0 Hz), 3.89 (s, 3H), 4.43 (t, 2H, J = 6.0 Hz), 7.05 (s, 2H, J = 8.0 Hz), 7.41 (m, 2H), 7.59 (s, 1H), 7.64 (s, 1H), 9.87 (s, 1H); ¹³C NMR (CDCl₃): δ 32.61, 56.21, 71.65, 98.47, 113.47, 115.24, 115.68, 125.12, 130.89, 131.97, 142.52, 151.87, 153.21, 187.47; IR: 3069, 2840, 2231, 1861, 1700, 1490, 1389, 1301, 1227, 1144, 1076, 970, 870, 631 cm⁻¹; Mass (70 ev): 332 (M⁺), 331, 292, 277, 239, 177, 176, 155, 127, 83, 63; HRMS: m/z Calcd for C₁₇H₁₇O₃SNF: 331.3457; Found: 331.3465.

References