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SOLVENT-FREE MICROWAVE ASSISTED SYNTHESIS OF 1-{6-BENZOYL-3-[(*E*)-2-(ARYL)-1-ETHENYL]-5-METHYLFURO [3′,2′: 4,5] BENZO [*b*] FURAN-2-YL}-1-ETHANONES AND THEIR ANTIBACTERIAL ACTIVITY

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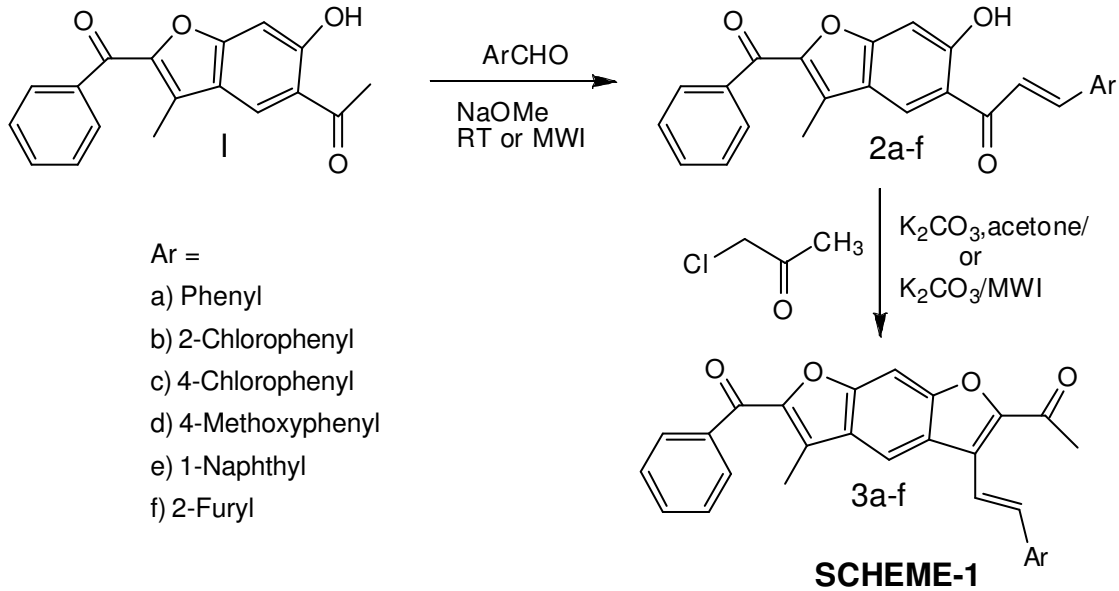
A series of 1-{6-benzoyl-3-[(*E*)-2-(aryl)-1-ethenyl]-5-methyl furo [3′,2′;4,5] benzo [*b*] furan-2-yl}-1-ethanones (**3**a-f) were synthesized by reacting (*E*)-1-(2-benzoyl-6-hydroxy-3-methylbenzo [*b*] furan-5-yl)-3-aryl-2-propen-1-ones (**2**a-f) with 2-chloroacetone in the presence of anhyd K_2CO_3 under solvent-free microwave irradiation. All the synthesized compounds were characterized by means of their IR, ^{1}H NMR, ^{13}C NMR, mass and elemental analysis. All the compounds were screened for their antibacterial activity.

Benzofuran derivatives have been shown to exhibit antiinflammatory[1,2], anticancer[3,4], antibacterial[5], antifungal[6], analgesic[7], antihistaminic[8], anti-HIV[9] and anticonvulsant[10] properties. Benzodifuran ring system exhibits interesting biological properties such as antibacterial[11-13], antifungal[11] and antiimplantation[11] activities. Styryl-based compounds showed good potential candidates for β-amyloid plaque imaging agents[14]. In recent years reports on microwave assisted synthesis revealed that it is safe, rapid, economic and environmental benign synthesis. Owing to increased regulatory pressure in research and industry, tremendous efforts have been made to reduce the amount of pollutants produced, including organic solvents in chemical synthesis. To secure such practice, the discovery and invention of new synthetic methods are required. Motivated by the potential bioactivity of benzofurans, benzodifurans, styryl moieties and also in contribution to our work[15] on microwave assisted synthesis of biologically important condensed heterocycles herein we wish to report the synthesis of some new styryl benzodifurans *viz*., 1-



Ar =
a) Phenyl
b) 2-Chlorophenyl
c) 4-Chlorophenyl
d) 4-Methoxyphenyl
e) 1-Naphthyl
f) 2-Furyl

SCHEME-1

Table-1
Physical data of 1-{6-benzoyl-3-[(*E*)-2-(aryl)-1-ethenyl]-5-methyl furo [3′,2′; 4,5]-benzo [*b*] furan-2-yl}-1-ethanones (3a-f)

Compd	M.P. (^{0}C)	Conventional method		Microwave method	
		Time (hr)	Yield (%)	Time (min)	Yield (%)
3a	218	8	64	6	82
3b	222	8	62	5	87
3c	>300	8	66	5	79
3d	>300	9	69	6	82
3e	230	10	66	5	84
3f	228	8	70	5	86

[{6-benzyl-3-[*E*]-2-(aryl)-1-ethenyl]-5-methylfuro [3′,2′;4,5] benzo [*b*] furan-2-yl}-1-ethanones (**3**a-f) under conventional and solvent-free microwave irradiation methods with a view to evaluate their antibacterial activity and ease of formation under microwave irradiation.

A literature survey revealed that styryl benzofurans[16,17] are prepared by refluxing 2-hydroxychalcones with 2-bromoacetophenone in organic solvents such as acetone, benzene and in the presence of base such as anhydrous potassium carbonate or phase transfer catalyst such as tetrabutyl ammonium hydrogen sulphate. These protocols required long reaction period. Based on previous studies to develop new protocol, we have studied the solvent free synthesis of 1-{6-benzoyl-3-[(*E*)-2-(aryl)-1-ethenyl]-5-methylfuro [3′,2′;4,5] benzo [*b*] furan-2-yl}-1-ethanones (**3**a-f) using anhydrous potassium carbonate as readily available green and inexpensive catalyst. The required precursors, (*E*)-1-(2-benzoyl-6-hydroxy-3-methylbenzo [*b*] furan-5-yl)-3-aryl-2-propen-1-ones[18] (**2**a-f) were synthesized by reacting 5-acetyl-2-benzoyl-6-hydroxy-3-methylbenzofuran[19] with aromatic/heteroaromatic aldehydes in the presence of sodium methoxide under microwave irradiation. The targeted compounds 1-{6-benzoyl-3-[(*E*)-2-(aryl)-1-ethenyl]-5-methylfuro [3′,2′;4,5] benzo [*b*] furan-2-yl}-1-ethanones (**3**a-f) were synthesized with good yields by reacting (*E*)-1-(2-benzoyl-6-hydroxy-3-methylbenzo [*b*] furan-5-yl)-3-aryl-2-propen-1-ones (**2**a-f) with 2-chloroacetone in the presence of anhydrous K_2CO_3 under conventional and microwave irradiation (Scheme-1). The advantages obtained by the use of microwave irradiation in relation to a conventional method were demonstrated (Table-1).

Antibacterial activity

All the compounds were screened for their antibacterial activity against bacterial strains such as *Bacillus subtilis* (ATCC-6633), *Staphylococcus aureus* (ATCC-29737), *Escherichia coli* (ATCC-10536) and *Pseudomonas aeruginosa* (ATCC-27853) using streptomycin, tetracycline, chloramphenicol, carbenicillin respectively as standard drugs. The activity was determined using cup-plate agar diffusion method[20] by measuring the inhibition zone in mm. Nutrient agar was used as a culture medium. A 1μg/ml solution in dimethylformamide was used. The agar medium was inoculated with bacterial cultures tested. After 24 hr of incubation at 37^0, the diameter of inhibition zone (in millimeters) was measured. Among the compounds screened **3**a, **3**b, **3**c, **3**d and **3**f showed good activity against all bacteria. The remaining compound **3**e was found to be moderately active against all bacteria.

Experimental

Melting points were determined in open capillaries and are uncorrected. The purity of the compounds was checked by TLC using the precoated silica gel plates $60F_{254}$ (Merck). Microwave reactions were carried out in Milestone Multi SYNTH microwave

system. IR spectra were recorded on Shimdazu FTIR 8400s spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Avance 300 spectrometer and mass spectra were recorded on Shimadzu mass spectrometer. Elemental analysis was determined by using Thermofinnigan CHNS analyzer.

Synthesis of 1-{6-benzoyl-3-[(*E*)-2-(aryl)-1-ethenyl]-5-methyl furo [3′,2′;4,5] benzo [*b*] furan-2-yl}-1-ethanones (3a-f) : General procedure

Conventional heating method

A mixture of **2**a-f (0.001 mol), 2-chloroacetone (0.001 mol) and anhydrous potassium carbonate (0.05g) in acetone (10 ml) was taken in to 50 ml round bottomed flask and it was refluxed for 8-10 hrs. Progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, acetone was distilled under vacuum and chilled water was added to the residue. The precipitate formed was filtered, washed with water and recrystallized from acetonitrile as yellow solid.

Microwave irradiation method

A thoroughly blended mixture of **2**a-f (0.01 mol), 2-chloroacetone (0.001 mol) and anhydrous potassium carbonate (2.5g) was taken into a quartz tube and inserted into a Teflon vial with screw capped and then subjected to microwave irradiation at the constant temp 120^0. After completion of the reaction, it was diluted with chilled water and the precipitate formed was filtered, washed with water and recrystallized from acetonitrile as yellow solid.

3a: IR (KBr): 3056, 3024, 2962, 2916, 2848, 1668, 1647, 1631, 1622, 1596, 1568, 1541, 1496, 1448, 1423, 1363, 1326, 1298, 1274, 1259, 1232, 1215, 1164, 1130, 1112, 1020, 972, 962, 939, 929 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.59 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 7.22-7.38 (m, 8H, ArH), 7.43 (s, 1H, Ar-H), 7.56 (d, 1H, α-H), 7.62 (d, 1H, β-H), 7.93-8.01 (m, 2H, ArH), 8.25 (s, 1H, Ar-H), MS : $[M+H]^+$ m/z 421 (30%). [Found : C, 79.88, H, 4.82 $C_{28}H_{20}O_4$ requires C, 80.00, H, 4.76%].

3b: IR (KBr): 3095, 3076, 2962, 1676, 1647, 1627, 1598, 1560, 1541, 1467, 1448, 1429, 1363, 1332, 1305, 1269, 1234, 1217, 1217, 1166, 1139, 1130, 1114, 1027, 975, 962, 939, 927. ^{1}H NMR (300 MHz, DMSO-d_6): 2.59 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 7.44 (d, 1H, α-H), 7.72 (d, 1H, β-H), 7.30-7.70 (m, 7H, ArH), 7.75 (s, 1H, C_4-H), 8.10 (d, 2H, ArH), 8.40 (s, 1H, C_8-H). MS : $[M+H]^+$ m/z 455 (30%). [Found : C, 73.85, H, 4.25 $C_{28}H_{19}ClO_4$ requires C, 73.92, H, 4.18%].

3c: IR (KBr): 3092, 3070, 2957, 2921, 1673, 1640, 1630, 1617, 1598, 1576, 1560, 1540, 1534, 1529, 1490, 1430, 1425, 1364, 1332, 1298, 1234, 1215, 1138, 1130, 1114, 1088, 974, 929. ^{1}H NMR (300 MHz, DMSO-d_6): 2.63 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 7.52 (d, 2H, ArH), 7.58-7.65 (m, 3H, ArH), 7.70 (d, 2H, α-H, β-H), 7.76 (d, 2H, ArH), 7.83 (s, 1H, C_8-H), 7.88 (s, 1H, C_4-H), 7.97-8.04 (m, 2H, ArH). MS : $[M+H^+]$, m/z 455 (50%). [Found : C, 73.89, H, 4.23 $C_{28}H_{19}ClO_4$ requires C, 73.92, H, 4.18%].

3d: IR (KBr): 3093, 3078, 3066, 3029, 3001, 2943, 2908, 2840, 1668, 1645, 1631, 1602, 1569, 1537, 1467, 1450, 1421, 1367, 1328, 1307, 1280, 1247, 1218, 1172, 1128, 1116, 1081, 975, 958, 927. ^{1}H NMR (300 MHz, DMSO-d_6): 2.57 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.95 (d, 1H, α-H), 7.40-7.54 (m, 7H, ArH), 7.61 (s, 1H, ArH), 7.83 (d, 1H, β-H), 7.98 (d, 2H, ArH), 8.28 (s, 1H, ArH). MS : $[M+H^+]$, m/z 451 (30%). [Found : C, 77.45, H, 4.89 $C_{29}H_{22}O_5$ requires C, 77.33, H, 4.88%].

3e : IR (KBr): 3078, 3056, 2962, 1667, 1649, 1628, 1597, 1572, 1559, 1545, 1507, 1445, 1428, 1328, 1305, 1264, 1229, 1217, 1125, 1112, 1089, 971, 958, 938. ^{1}H NMR (300 MHz, DMSO-d_6): 2.64 (s, 3H, CH_3), 2.67 (s, 3H, CH_3), 7.56-7.63 (m, 4H, ArH), 7.65-7.75 (m, 4H, ArH), 7.70 (d, 1H, α-H), 7.90 (d, 1H, β-H), 8.15 (d, 1H, ArH), 8.38 (d, 2H, ArH), 8.56 (d, 1H, ArH), 8.64 (d, 1H, ArH), 8.78 (d, 1H, ArH). MS: $[M^+]$, m/z 470 (100%). [Found : C, 81.62, H, 4.77 $C_{32}H_{22}O_4$ requires C, 81.62, H, 4.77%].

3f : IR (KBr): 3153, 3120, 3072, 1668, 1649, 1616, 1598, 1573, 1533, 1471, 1471m 1446, 1429, 1363, 1350, 1328, 1307, 1280, 1234, 1218, 1126, 1085, 1012, 941, 925. ^{1}H NMR (300 MHz DMSO-d_6): 2.48 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 6.63 (d, 1H, β-H, furyl), 6.76 (d, 1H, β-H, furyl), 7.58-7.91 (m, 7H, ArH & α-H, β-H), 8.04 (d, 2H, ArH), 8.65 (s, 1H, C_8-H, ArH). ^{13}C NMR (75MHz, DMSO-d_6): 10.08, 28.08, 95.80, 111.92, 112.42, 116.14, 122.89, 123.16, 126.79, 127.11, 128.59, 129.25, 132.89, 137.40, 138.10, 144.14, 148.55, 152.52, 153.92, 154.39, 185.05, 190.56. MS : $[M+H^+]$, m/z 411 (100%). [Found : C, 76.28, H, 4.40 $C_{26}H_{18}O_5$ requires C, 76.09, H, 4.39%].

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