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Synthesis of 2,3-diphenyl-5-methyl-6-aroylbenzo[1,2-*b*:5,4-*b'*]difurans under PTC conditions and their anti-microbial activity

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2,3-Diphenyl-6-hydroxybenzofuran **1** and 2,3-diphenyl-5-acetyl-6-hydroxybenzofuran **3** have been synthesized under microwave irradiation. 2,3-Diphenyl-5-acetyl-6-aroylbenzo[1,2-*b*:5,4-*b'*]difurans **5a-h** and **6a-e** have been synthesized from the reaction of **3** and phenacyl bromides **4a-h** under PTC conditions using $TBAHSO_4$ (Tetrabutylammonium hydrogen sulphate) as a catalyst in good yields. The compounds **5a-h** and **6a-e** have been screened for antibacterial and antifungal activities. Compounds **5b** and **5e** have shown maximum inhibitory activity against *E. coli* and *S. aureus*, while compounds **5b**, **5e-g** and **6a** show maximum spore germination inhibition against *Fusarium moniforme*.

Benzofurans[1], benzodifurans[2], aroylbenzodifurans[3], tetraarylbenzodifurans[4] are gaining importance in recent years as anti-implantation, antimicrobial and photochromic agents. Our studies on cyclised triaryl ethylene systems as anti-implantation agents [5-6] and also which are considered to be anti-cancer agents[7-9], encouraged us to undertake the synthesis and antimicrobial activity of 2,3-diphenyl-5-methyl-6-aroylbenzo[1,2-*b*:5,4-*b'*]difurans **5a-h** and **6a-e**.

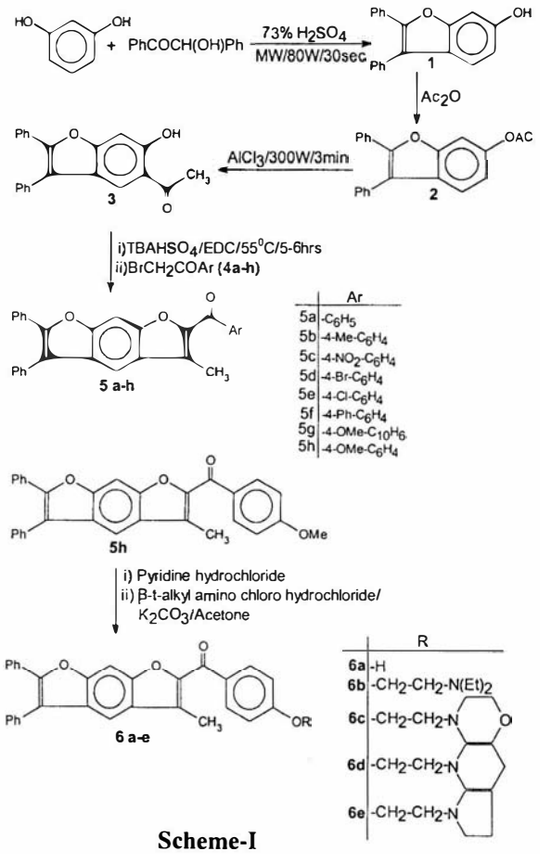
Results and Discussion

The syntheses of 2,3-diphenyl-5-acetyl-6-hydroxybenzofuran **3** and 2,3-diphenyl-6-hydroxy benzofuran **1** were reported by earlier workers in poor yields[10]. We have modified the synthesis of compound **1** which is formed within 30 seconds under microwave irradiation at power level 80 watt in 90% yield. Compound **1** on treatment with Ac_2O gave its acetyl derivative **2** which on Fries migration in anhydrous $AlCl_3$ and toluene under microwave irradiation at power level 300 watt furnished **3** within 3 min. The aroylbenzodifurans **5a-h** were synthesized from the reaction of **3** and $BrCH_2COAr$ **4a-h** under PTC conditions[11] at 55-60°C in the presence of K_2CO_3 in EDC. Similarly, compound **5h** was demethylated in pyridine hydrochloride to get **6a**. The compound **6a** when treated with β-tertiaryalkylaminochloro hydrochlorides in anhydrous K_2CO_3 and acetone gave **6b-e**. The reaction sequence is depicted in **Scheme I**.

It is also observed that excellent yields of benzodifurans were obtained when simple and substituted phenacyl bromides were treated with compound **3**. The yields of benzodifurans **5c** and **5h** were slightly decreased when 4-nitrophenacyl and 4-methoxyphenacyl bromides were used.

The compounds **5a-h** and **6a-e** were characterized by UV, IR, NMR and mass spectral data. The UV spectra of **5a-h** and **6a-e** displayed two absorption bands in the regions λ_{max} 307 and 336 nm as compared to the unsubstituted benzofuran[12], which showed three absorption bands at λ_{max} 245, 275 and 282 nm. It is evident that all the bands in these benzodifurans **5a-h** and **6a-e** are observed at longer wavelength regions. This bathochromic shift is due to the presence of a second furan ring and one aroyl group and two phenyl groups, which facilitate the extended conjugation. The IR spectra of **5a-h** and **6a-e** showed three bands at 1676 (C=O str.), 1600 (C=C str.) and 1240-1260 cm^{-1} (C-O-C str.). In ^1H NMR spectra of compounds **5a-h** and **6a-e** the methyl protons attached to the furan ring at 5th position were observed[13] as singlet at δ 2.2, while in compound **3** the methyl protons of $-CO-CH_3$ group appeared[14] as singlet at δ 2.6. The ring closure and linear nature of the benzodifurans was confirmed by the following observations in the compounds **5a-h** and **6a-e**.

(i) The 11 protons at C4 and 2,3-diphenyl groups were observed as multiplet at δ 7.2-7.5.



Scheme-I

(ii) The proton at C-8 was observed as singlet at δ 6.74-7.56, while in compound **3** the C-7 proton appeared as a singlet at δ 6.9.

(iii) The 2 protons adjacent to aroyl group i.e., C-2′,6′ were observed as doublet at δ 8.0.

(iv) The 2 protons adjacent to aroyl group i.e., C-3′,5′ were observed as doublet at δ 7.08.

Antimicrobial activity

Compounds **5a-h** and **6a-e** were screened *in vitro* against pathogenic bacteria *Escherichia coli* and *Staphylococcus aureus* at 10μg/mL and 20μg/mL in DMF using cup-plate agar diffusion method[15], the zone of inhibition measured in cm. The compounds **5b** and **5e** were active against *E. coli* and *S. aureus*. *p*-Methyl group in **5b** and *p*-chloro group in **5e** imparted for their inhibitory activity against *E. coli* and *S. aureus*, while other compounds were inactive against *E. coli* and *S. aureus* in the series. The antibacterial activity was compared with the known antibiotics, viz. Ampicillin, Chloramphenicol and the results are presented in **Table I**.

Compounds were also screened for their antifungal activity against *Fusarium moniforme* at 120 μg/mL, 360 μg/mL, 600 μg/mL and 840 μg/mL concentrations using the glass slide humid chamber technique[16]. Compounds **5b** (98%), **5e** (97%), **6a** (97%), **5f** (96%), **5h** (95%) showed maximum spore germination inhibition at higher concentrations. The antifungal activity was compared with the known antibiotics, viz. Griseofulvin, Dichloran and the results are presented in **Table II**.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. The UV spectra were recorded on a Shimadzu UV 160A UV-Vis-NIR spectrophotometer; IR spectra on a Shimadzu FTIR model 8010 spectrophotometer; ^{1}H NMR spectra in $CDCl_3$ on a Varian C_{17}-20-ZM-390-20 MHz NMR spectrophotometer using TMS as an internal standard and mass spectra on EIMS at 70 eV. The C, H, N, S and O analysis of compounds were done on a Carlo Erba Model EA 1108 CHNS-O elemental analyser.

Table I—Zone of inhibition at different concentrations against *E. coli* and *S. aureus*

	E. coli		*S. aureus*	
	10 μg/mL	20 μg/mL	10 μg/mL	20 μg/mL
5b	1.4 cm	1.5 cm	1.3 cm	1.5 cm
5e	1.0 cm	1.2 cm	0.9 cm	1.1 cm
Ampicillin	1.8 cm	2.3 cm	1.3 cm	1.8 cm
Chloramphenicol	1.2 cm	1.6 cm	1.3 cm	1.7 cm

Table II–Percentage of spore germination inhibition at different concentrations against *F .moniforme*

Compd	Concentration			
	120μg/mL	360μg/mL	600μg/mL	840 μg/mL
5b	80%	82%	91%	98%
5c	78%	79%	81%	85%
5d	79%	82%	85%	88%
5e	80%	82%	90%	97%
5f	83%	89%	91%	96%
5g	71%	74%	78%	79%
5h	79%	85%	91%	95%
6a	90%	82%	93%	97%
Griseofulvin	92%	94%	95%	99%
Dichloran	85%	88%	91%	95%

Synthesis of 2,3-diphenyl-6-hydroxybenzofuran 1 under microwave irradiation. Resorcinol (0.01 mole, 1.1g) and benzoin (0.01 mole, 2.12 g) were intimately mixed and melted on hotplate. To this 73% H_2SO_4 (5 mL) was added and irradiated in a microwave oven for 30 sec at 80 watt level. The solid obtained was cooled and poured in water, washed with 5% NaOH and water, filtered, dried and recrystallized from ethanol, mp 63° C, yield 90%(2.34g).

2,3-Diphenyl-5-acetyl-6-hydroxybenzofuran 3 by Fries migration under microwave irradiation. 2,3-Diphenyl-6-acetoxybenzofuran[10] **2** (0.01 mole, 3.38 g) in anhydrous $AlCl_3$ (6 g) intimately mixed in toluene (20mL) was irradiated in microwave oven for about 3 min at 300 watt power level. The solid obtained was cooled and decomposed with ice and HCl. The excess solvent was recollected under reduced pressure and the product obtained was recrystallized from boiling naphtha, mp 154° C, yield 80%(2.70 g). It was compared with authentic sample by co-TLC and mixture melting point.

2, 3-Diphenyl-5-methy-6-aroylbenzo[1,2-*b*:5,4-*b*']-difuran 5a-h under PTC conditions. To a magnetically stirred solution of 2,3-diphenyl-5-methyl-6-acetylbenzofuran (0.01 mole, 3.38 g) in EDC (30mL), 20% K_2CO_3 (30 mL) and $TBAHSO_4$ (100mg) were added. The reaction mixture was heated to 50° C and phenacyl bromide 4a-h (0.01 mole) dissolved in 10mL EDC was added dropwise over a period of 30 min at 55-60° C and stirred for 5-6 hr. The organic layer was separated and washed with 5% NaOH solution and then with water. The resulting organic layer was dried over anhydrous Na_2SO_3. The excess solvent was removed under reduced pressure and the crude product was recrystallized from aqueous dioxan.

2, 3-Diphenyl-5-methyl-6-(4-hydroxybenzoyl)-benzo[1,2-*b*:5,4-*b*']difuran 6a. Compound **5h** (0.01 mole, 4.58 g) and freshly distilled pyridine hydrochloride (0.01 mole, 11.5g) were heated at 220°C for 30 min. The reaction mixture was cooled, decomposed with water, filtered and the crude product obtained was recrystallized from aqueous dioxan.

2, 3-Diphenyl-5-methyl-6-(*p*-β-diethylaminoethoxybenzoyl)benzo[1,2-*b*:5,4-*b*']difuran 6b. A mixture of compound **6a** (0.01 mole, 4.44 g), diethylamino ethylchloro hydrochloride (0.01 mole, 1.72 g) in anhydrous K_2CO_3 (5 g) and dry acetone (300mL) was refluxed for 20 hr. The reaction mixture was filtered and concentrated to yield **6b**, which was recrystallized from aqueous dioxan.

Compounds **6c-e** were prepared similarly.

2, 3-Diphenyl-5-methyl-6-benzoylbenzo [1, 2-*b*: 5,4-*b*'] difuran 5a: mp 135°, yield 85%; UV (MeOH): 308 and 340 nm; IR (cm^{-1}): 1647, 1564, 1257 and 866; MS m/z (%): M^+, 428 (6), 105 (100) and 77 (74); ^1H NMR ($CDCl_3$): δ 2.2 (s, 3H, 5-CH_3), 6.75 (s, 1H, C-8H), 7.08 (m, 3H, H-3′,4′,5′), 7.4 (m, 11H, C-4H and Ar-H), 7.9 (m, 2H,H-2′,6′); Anal. Calc. for $C_{30}H_{20}O_3$ (428): C, 84.12; H, 4.6. Found: C, 84.08; H, 4.65%.

2, 3-Diphenyl-5-methyl-6-(*p*-methylbenzoyl)-benzo [1,2-*b*:5,4-*b*'] difuran 5b: mp 140°, yield 80%; UV(MeOH): 309 and 334 nm; IR (cm^{-1}): 1678, 1600.8, 1261.4 and 840; MS m/z (%): M^+, 442 (5), 313 (27), 119 (80), 105 (25) and 77(75); ^1H NMR($CDCl_3$): δ 2.2 (s, 3H, 5-CH_3), 2.7(s, 3H, 4′-CH_3), 6.75 (s, 1H, C-8H), 7.4 (m, 11H, C-4H and Ar-H), 8.1 (d, 2H, H-3′, 5′, *J*=9Hz), 8.0 (d, 2H, H-2′,6′, *J*=9Hz); Anal. Calc. for $C_{31}H_{22}O_3$(442): C,84.16; H,4.77. Found: C,84.12; H,4.73%.

2, 3-Diphenyl-5-methyl-6-(*p*-nitrobenzoyl)benzo-[1,2-*b*:5,4-*b*'] difuran 5c: mp 215°, yield 75%; UV(MeOH): 308 and 336 nm; IR (cm^{-1}): 1640, 1600, 1250,and 852; ^1H NMR($CDCl_3$): δ 2.2 (s, 3H, 5-CH_3), 7.0 (s, 1H, C-8H), 7.4 (m, 11H, C-4H and Ar-H), 8.1 (d, 2H, H-3′,5′, *J*=9Hz), 8.0 (d, 2H, H-2′,6′, *J*=9Hz); Anal. Calc. for $C_{30}H_{19}O_5N$ (473): C,76.10; H,4.01; N, 2.95. Found: C, 76.06; H,4.03; N,2.89%.

2, 3-Diphenyl-5-methyl-6-(*p*-bromobenzoyl)-benzo [1,2-*b*:5,4-*b*'] difuran 5d: mp 155°, yield 85%; UV(MeOH): 307 and 337 nm; IR (cm^{-1}): 1703, 1585, 1257 and 827; ^1H NMR($CDCl_3$): δ 2.3 (s, 3H, 5-CH_3), 7.0 (s, 1H, C-8H), 7.4 (m, 11H, C-4H and Ar-H), 6.9 (d, 2H, H-3′,5′, *J*=9Hz), 8.0 (d, 2H, H-2′,6′, *J*=9Hz); Anal. Calc. for $C_{30}H_{19}O_3N$(507): C, 71.5; H,3.74; Br, 15.77. Found: C, 71.2; H, 3.69; Br, 15.71%.

2, 3-Diphenyl-5-methyl-6-(*p*-chlorobenzoyl)-benzo [1,2-*b*:5,4-*b*'] difuran 5e: mp 158°, yield 80%; UV(MeOH): 307 and 336 nm; IR(cm^{-1}): 1680, 1591, 1224 and 833; MS m/z (%): M^+, 462(6), 313 (27), 139(100), 111(42), 105(56) and 77 (74); ^1H NMR ($CDCl_3$): δ 2.2 (s, 3H, 5-CH_3), 6.74 (s, 1H, C-8H), 6.9 (d, 2H, H-3′,5′, *J*=9Hz), 8.1 (d, 2H, H-2′,6′, *J*=9Hz), 7.4 (m, 11H, C-4H and Ar-H); Anal. Calc. for $C_{30}H_{19}O_3Cl$ (462.5): C,77.83; H,4.1; Cl, 7.67. Found: C,77.82; H,3.9; Cl, 7.63%.

2,3-Diphenyl-5-methyl-6-(*p*-methoxynaphthoyl)-benzo [1,2-*b*:5,4-*b*'] difuran 5f: mp 136°, yield 75%; UV(MeOH): 305 and 335nm; IR(cm^{-1}): 1670, 1622,

1588, 1271 and 904; ^{1}H NMR ($CDCl_3$): δ2.2 (s, 3H, 5-CH_3), 4.1 (s, 3H, 4′-OCH_3), 6.7 (s, 1H, C-8H), 7.4 (m, 15H, C-4H and Ar-H); Anal. Calc. for $C_{35}H_{22}O_4$ (508): C,82.67; H,4.72. Found: C,82.53; H,4.62%.

2, 3-Diphenyl-5-methyl-6-(*p*-phenylbenzoyl)-benzo [1,2-*b*:5,4-*b*′] difuran 5g: mp 193°, yield 75%; UV(MeOH): 308 and 336nm; IR(cm^{-1}): 1676, 1610, 1582, 1271 and 902; ^{1}H NMR ($CDCl_3$): δ 2.2 (s, 3H, 5-CH_3), 7.1 (m, 2H, H-2′ ,6′), 6.57 (s, 1H, C-8H), 7.4 (m, 18H, C-4H, H-3′ ,5′ and Ar-H); Anal. Calc. for C_{36} H_{24} O_3 (504): C, 85.71; H,4.76. Found: C,85.69; H,4.75%.

2, 3-Diphenyl-5-methyl-6-(*p*-methoxybenzoyl)-benzo [1,2-*b*:5,4-*b*′] difuran 5h: mp 155°, yield 65%; UV(MeOH): 307 and 336nm; MS m/z (%): M^+, 458(7), 135(100), 107 (12),77 (74); IR (cm^{-1}): 1676, 1610, 1582, 1271 and 902; ^{1}H NMR($CDCl_3$): δ 2.2 (s, 3H, 5-CH_3), 3.9 (s, 3H, 4′-OCH_3), 6.57 (s, 1H, C-8H), 7.0 (d, 2H, H-3′ ,5′, *J*=9Hz), 8.05 (d, 2H, H-2′ ,6′, *J*=9Hz), 7.4 (m, 11H, C-4H and Ar-H); Anal. Calc. for $C_{31}H_{22}O_4$ (458): C,81.22; H,4.80. Found: C,81.10; H,4.78%.

2, 3-Diphenyl-5-methyl-6-(*p*-hydroxybenzoyl)-benzo[1,2-*b*:5,4-*b*′]difuran 6a: mp 225°, yield 75%; UV(Dioxan): 306 and 337nm; IR(cm^{-1}): 3300, 1670, 1600.8, 1573, 1255 and 837; ^{1}H NMR ($CDCl_3$): δ2.2 (s, 3H, 5-CH_3), 7.54 (s, 1H, C-8H), 6.9 (d, 2H, H-3′ ,5′, *J*=9Hz), 8.02 (d, 2H, H-2′ ,6′, *J*=9Hz), 10.5 (s, 1H, 4′-OH, D_2O exchangeable), 7.4 (m, 11H, C-4H and Ar-H); Anal. Calc. for $C_{30}H_{20}O_4$ (444): C, 81.08; H,4.50. Found: C, 80.92; H,4.41%.

2, 3-Diphenyl-5-methyl-6-(*p*-β-diethylaminoeth-oxybenzoyl)benzo[1,2-*b*:5,4-*b*′] difuran 6b: mp 125°, yield 75%; UV(Dioxan): 306 and 338nm; IR(cm^{-1}): 2925, 1676, 1600.8, 1575, 1255 and 840; ^{1}H NMR($CDCl_3$): δ 2.2 (s, 3H, 5-CH_3), 6.8 (s, 1H, C-8H), 6.68 (d, 2H, H-3′ ,5′, *J*=9Hz), 7.4 (m, 11H, C-4H and Ar-H), 8.0 (d, 2H, H-2′ ,6′, *J*=9Hz), 3.94 (t, 2H,-OCH_2, *J*=6Hz), 2.77 (t, 2H,-CH_2-N, *J*=6Hz), 1.02 (t, 6H,-N(CH_3)$_2$, *J*=7.5Hz), 2.53-2.6 (m, 4H, -N(CH_2)$_2$); Anal. Calc. for $C_{36}H_{33}NO_4$ (543): C, 79.55; H,6.07; N,2.57. Found: C, 79.53; H, 6.03; N, 2.54%.

2,3-Diphenyl-5-methyl-6-(*p*-β-morpholinoethoxy-benzoyl) benzo [1,2-*b*:5,4-*b*′] difuran 6c: mp 198°, yield 80%; UV(Dioxan): 306 and 337nm; IR(cm^{-1}): 2920, 1670, 1600.8, 1575 and 840; ^{1}H NMR($CDCl_3$): δ 2.2 (s, 3H, 5-CH_3), 6.9 (d, 2H, H-3′ ,5′, *J*=9Hz), 7.56 (s, 1H,C-8H), 7.4 (m, 11H, C-4H and Ar-H), 8.0 (d, 2H, H-2′ ,6′, *J*=9Hz), 2.56-3.0 (m, 4H,-N(CH_2)$_2$), 4.20 (m, 4H, O-(CH_2)$_2$), 4.0 (t, 2H, OCH_2, *J*=6Hz), 3.0(t, 2H,-CH_2-N, *J*=6Hz); Anal. Calc. for $C_{36}H_{31}NO_5$ (557): C, 77.55; H,5.56; N,2.51. Found: C, 77.51; H, 5.52; N, 2.49%.

2, 3-Diphenyl-5-methyl-6-(*p*-β-piperidinoethoxy-benzoyl) benzo [1,2-*b*:5,4-*b*′] difuran 6d: mp 178°, yield 80%; UV (Dioxan): 305 and 338nm; IR(cm^{-1}): 2920, 1670, 1600, 1570 and 830; ^{1}H NMR($CDCl_3$): δ 2.2 (s, 3H, 5-CH_3), 2.5 (m, 4H, C-2",6"-H), 2.9 (t, 2H,-CH_2-N, *J*=6Hz), 4.1(t, 2H,-OCH_2, *J*=6Hz), 7.3 (s, 1H, C-8H), 7.4 (m, 11H, C-4H and Ar-H), 6.8 (d, 2H, H-3′ ,5′, *J*=9Hz), 8.3 (d, 2H, H-2′ ,6′, *J*=9Hz), 1.62 (m, 6H, C-3", 4", 5"-H); Anal. Calc. for $C_{37}H_{33}NO_4$ (555): C, 80.00; H,5.94; N,2.50. Found: C, 79.80; H, 5.91; N, 2.48%.

2,3-Diphenyl-5-methyl-6-(*p*-β-pyrrolidinoethoxy-benzoyl) benzo [1,2-*b*:5,4-*b*′] difuran 6e: mp 266°, yield 85%; UV(Dioxan): 305 and 335nm; IR(cm^{-1}): 2925, 1676, 1600, 1575, and 840; ^{1}H NMR($CDCl_3$): δ 2.2 (s, 3H, 5-CH_3), 2.5 (m, 4H, C-2", 5"-H), 2.9 (t, 2H,-CH_2-N, *J*=6Hz), 4.1 (t, 2H,-OCH_2, *J*=6Hz), 7.1 (s, 1H, C-8H), 7.4 (m, 11H, C-4H and Ar-H), 6.8 (d, 2H,C-3′,5′, *J*=9Hz), 8.3 (d, 2H, H-2′ ,6′, *J*=9Hz), 1.69 (m, 4H, C-3", 4"-H); Anal. Calc. for $C_{36}H_{31}NO_4$ (541): C, 79.85; H,5.73; N,2.58. Found: C, 79.81; H, 5.71; N, 2.55%.

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