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Note

Synthesis of biologically active angularly fused bisaroylbenzodifurans by PTC and solvent free microwave irradiation

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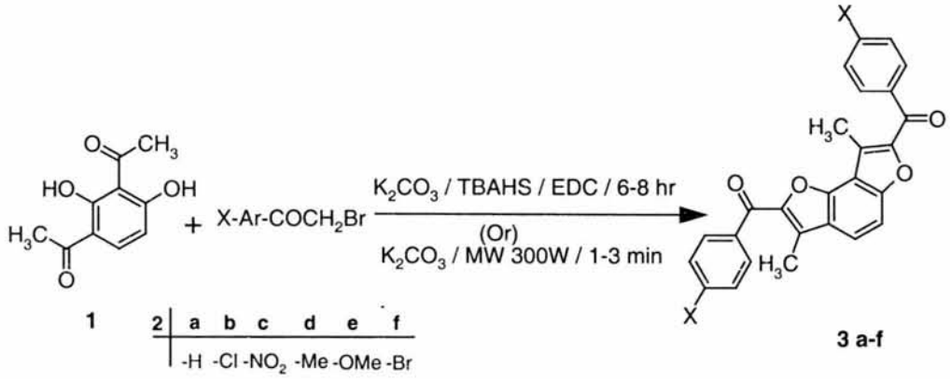
Angularly fused bisaroylbenzodifurans **3a-f** have been synthesized by condensing 2,4-diacetyl resorcinol **1** with various *p*-substituted phenacyl bromides **2a-f** under (a) phase transfer catalysis method and (b) microwave irradiation method. A comparison has been made between the two methods. Microwave irradiation has been found to be an efficient route for the synthesis of angularly fused bisaroylbenzodifurans. All the compounds **3a-f** have been screened for anti-bacterial activity. The benzodifurans **3c** and **3f** have shown excellent activity against gram-positive (*Staphylococcus aureus*) bacteria at both 600 and 900 μg/mL and the compound **3b** and **3d** are found active at 900 μg/mL on the same bacteia. The bisaroylbenzodifurans **3a-f** have also been screened for anti-fungal activity. The compounds **3c**, **3d** and **3f** have shown maximum spore germination inhibition on *Drechslera halodes* fungi and the compounds **3a**, **3b**, **3c**, **3d**, and **3f** have shown maximum spore germination inhibition on *Fusarium oxysporum* fungi at 960 μg/mL . The bisaroylbenzodifurans **3a** and **3e** have been screened for anti-implantation activity as well and found to be inactive at 10 mg/kg/rat/day.

A large number of oxygen heterocyclics have been associated with biological activities[1-6] like, anti-inflammatory, analgesic, anti-spasmodic, coronary vasodilatory, dermal photosensitizing, anti-bacterial, anti-fungal, phototoxic, and anti-implantation activity. Naturally occurring furanocoumarin derivatives like psoralen, angelecin (isopsoralen) have also shown wide range of biological activities[7]. We have reported 100% anti-implantation activity of 2,6-dibenzoyl-3,5-dimethylbenzo[1,2-*b*'; 5,4-*b*'']difuran at 2 mg/kg/rat/day[8]. It was observed from the literature that angularly fused bisaroylbenzodifurans were not tested for the anti-bacterial and anti-fertility activities.

So, in the present communication, we have synthesized angularly fused bisaroylbenzodifuran molecules to evaluate their anti-bacterial and anti-implantation activities. Thus, the title compounds **3a-f** were synthesized by adopting our earlier reported procedure[8], by condensing 2,4-diacetyl resorcinol[9] **1** with various *p*-substituted phenacyl bromides[10-14] **2a-f** in the presence of aq. K_2CO_3 and tetrabutyl ammonium hydrogen sulphate (phase transfer catalyst) in ethylene dichloride as a solvent at 55-60°C for 6-8 hr (**Scheme I**).

In the last few years, there has been a growing interest in the use of microwave heating in organic synthesis. The use of such microwave reaction conditions reveals several features like short reaction time compared to conventional heating, ease of work-up after the reaction, and reduction in the usual thermal degradation and better selectivity.

Microwave ovens provide a clean and cheap alternative to conventional oil-baths. Microwave heating has been proven to be beneficial particularly for the reactions under "dry" media (i.e., in the absence of solvent, on solid support with or without catalyst). Liquid-Liquid extraction can be avoided for the



Scheme I

Table I—Characterization data of angular bisaroylbenzodifurans **3a-f**

Compd	m.p. °C	Mol. formula	PTC (hr)	Yield (%)	MW (min)	Yield (%)	Found (%)/ (Calcd) C	Found (%)/ (Calcd) H	UV (λ_{max}; nm)	^{1}H NMR (δ, ppm)	Mass (% of abundance)
3a	178-79	$C_{26}H_{18}O_4$	6.0	85.4	1.5	95.5	79.15 (79.17	4.54 4.60)	259, 325	8.2-8.1(d, 4H, $C_{2'6'2'',6''}$-H, *J*=9Hz); 7.6-7.5(m, 7H, $C_{3',4',5',3'',4'',5''}$ & C_4-H); 7.75(d, 1H, C_5-H, *J*=9Hz); 2.95(s, 3H, 8-CH_3); 2.75(s, 3H, 3-CH_3)	394(6), 366(24), 338(12), 158(34), 130(45), 105(100), 102(3), 77(52)
3b	211-12	$C_{26}H_{16}Cl_2O_4$	6.5	89.7	2.5	94.3	67.38 (67.40	3.45 3.48)	255, 324	8.15-8.1(d, 4H, $C_{2',6',2'',6''}$-H, *J*=9Hz); 7.6-7.5(m, 5H, $C_{3',5',3'',5''}$ & C_4-H); 7.7(d, 1H, C_5-H, *J*=9Hz); 2.9(s, 3H, 8-CH_3); 2.75(s, 3H, 3-CH_3)	---
3c	217-19	$C_{26}H_{16}N_2O_8$	7.5	80.0	3.0	90.0	64.45 (64.47	3.30 3.33)	260, 326	8.25-8.2(d, 4H, $C_{2',6',2'',6''}$-H, *J*=9Hz); 7.75-7.6(m, 5H, $C_{3',5',3'',5''}$ & C_4-H); 7.85(d, 1H, C_5-H, *J*=9Hz); 2.9(s, 3H, 8-CH_3); 2.85(s, 3H, 3-CH_3)	---
3d	216-17	$C_{28}H_{22}O_4$	6.0	87.6	2.5	93.2	79.58 (79.60	5.20 5.25)	260, 321	8.15-8.1(d, 4H, $C_{2',6',2'',6''}$-H, *J*=9Hz); 7.6-7.5(m, 5H, $C_{3',5',3'',5''}$ & C_4-H); 7.7(d, 1H, C_5-H, *J*=9Hz); 2.8(s, 3H, 8-CH_3); 2.75(s, 3H, 3-CH_3), 2.2(s, 6H, $C_{4',4''}$-CH_3)	---
3e	188-89	$C_{28}H_{22}O_6$	6.0	89.9	1.5	96.7	73.99 (74.00	4.85 4.88)	258, 322	8.05-8.0(d, 4H, $C_{2',6',2'',6''}$-H, *J*=9Hz); 7.5-7.4(m, 5H, $C_{3',5',3'',5''}$ & C_4-H); 7.6(d, 1H, C_5-H, *J*=9Hz); 4.0(s, 6H, OCH_3); 2.9(s, 3H, 8-CH_3); 2.75(s, 3H, 3-CH_3)	---
3f	180-81	$C_{26}H_{16}Br_2O_4$	7.0	89.0	2.0	95.0	56.50 (56.55	2.90 2.92)	260, 325	8.15-8.05(d, 4H, $C_{2',6',2'',6''}$-H, *J*=9Hz); 7.65-7.4(m, 5H, $C_{3',5',3'',5''}$ & C_4-H); 7.7(d, 1H, C_5-H, *J*=9Hz); 2.8(s, 3H, 8-CH_3); 2.75(s, 3H, 3-CH_3)	---

isolation of reaction products. Moreover, the absence of solvent reduces the risk of explosions when reaction takes place in a microwave oven.

Hence this method of synthesis was adopted for the first time for the synthesis of 2,7-di(*p*-substituted-benzoyl)-3,8-dimethylbenzo[1,2-*b*′; 3,4-b″]difurans **3a-f** for the better yields and is presented in this note. Thus 2,4-diacetylresorcinol **1** and various *p*-substituted phenacyl bromides **2a-f** were doped on K_2CO_3 and the mixture was irradiated in household microwave oven at 300W power level for a period of 1-3 min (**Scheme I**). After irradiation, the contents were poured in to water to get the crude product. The angular bisaroylbenzodifurans **3a-f** were obtained in pure form on crystallization from methanol. This method was compared with the above phase transfer catalysis method. The reduction in reaction time (1-3 min) and the simplicity in the isolation of pure compounds are the two major advantages of this technique. The yields of angular bisaroylbenzodifurans **3a-f** are relatively good. Their characterization data are given in **Table I**.

Results and Discussion

The angular bisaroylbenzodifurans **3a-f** were characterized by UV, IR, NMR, Mass spectra and elemental analysis (**Table I**). The UV spectra of all the compounds **3a-f** have displayed two absorption bands at 258-260 and 325-327 nm. In the IR spectra of all the bisaroylbenzodifurans **3a-f**, carbonyl stretching was observed at 1635-1670 cm^{-1} and the C=C stretching frequency was observed at 1550-1590 cm^{-1}. In the ^{1}H NMR spectra C_5 proton appeared as a doublet at δ 7.85-7.6 ppm. The four protons adjacent to aroyl

Table II—Anti-bacterial and anti-fungal activites of angular bisaroylbenzodifurans **3a-f**

Compd	Conc.	Anti-bacterial activity							
	μg/mL	*E. coli*	*P. vulgaris*	*K. pneumoniae*	*P. aeruginosa*	*S. citricus*	*S. aureus*	*B. subtilis*	*S. albus*
3a	600	NA	NA	NA	NA	NA	NA	NA	NA
	900	NA	NA	NA	NA	NA	NA	NA	NA
3b	600	3.84	1.96	2.82	1.96	1.96	1.96	1.96	2.82
	900	7.85	2.82	5.02	5.02	5.02	6.35	5.02	6.35
3c	600	1.25	0.70	0.31	1.25	1.96	5.02	5.02	1.96
	900	1.96	1.96	1.25	5.02	3.84	6.35	7.85	5.02
3d	600	3.84	1.96	2.82	1.96	1.96	1.96	1.96	2.82
	900	5.02	3.84	3.84	3.84	3.84	6.35	2.82	5.02
3e	600	1.96	1.96	1.25	1.96	2.82	2.82	1.96	1.25
	900	2.82	5.02	3.84	2.82	5.02	3.84	3.84	2.82
3f	600	0.70	1.96	1.25	5.02	3.84	6.35	5.02	1.96
	900	2.82	3.84	2.82	6.35	5.02	7.85	6.35	3.84
Streptomycin	600	6.75	4.74	4.76	NA	4.2	3.0	5.52	5.52
	900	10.1	5.05	10.1	NA	6.3	4.5	8.28	8.28

Compd	Conc.	Anti-fungal activity							
	μg/mL	*Drechslera halodes* fungi % of spore germination (μg/mL)				*Fusarium oxysporum* fungi % of spore germination (μg/mL)			
		160	320	640	960	160	320	640	960
3a	600	4.74	6.72	26.18	41.55	14.90	40.34	51.46	85.21
	900								
3b	600	3.59	12.79	23.06	56.04	7.82	19.94	35.59	71.49
	900								
3c	600	11.54	26.12	64.22	88.76	9.6	24.08	44.75	82.28
	900								
3d	600	6.11	18.95	28.96	78.89	11.14	24.32	44.30	81.70
	900								
3e	600	3.62	8.51	25.09	64.51	8.0	18.87	31.44	52.63
	900								
3f	600	63.38	25.52	51.35	90.96	10.67	26.40	51.18	73.91
	900								
Streptomycin	600	---	---	---	---	---	---	---	---
	900								

NA: No Activity

group i.e., $C_{2',6',2'',6''}$ were observed as doublet at δ 8.25-8.05 ppm. The protons at $C_{3',5',3'',5''}$ were observed as multiplet along with C_4-H at δ 7.4-7.75 ppm in the compounds **3b-f**. Whereas in **3a** one multiplet was observed at δ 7.6-7.5 ppm for protons at $C_{3',4',5',3'',4'',5''}$ and C_4.

Biological activity

Anti-bacterial activity

The angularly fused bisaroylbenzodifurans **3a-f** were tested on four gram-positive bacteria (*Staphylococcus citricus, Staphylococcus aureus, Bacillus subtilis, Streptococcus albus)* and also on four gram-negative bacteria (*Escherichia coli*, *Proteus vulgaris*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*) at concentrations 600 and 900 μg/mL, by adopting Vincent and Vincent[15] filter paper disc method. The results are depicted in **Table II**.

The 2,7-di(*p*-bromobenzoyl)-3,8-dimethylbenzo-[1,2-*b*'; 3,4-*b*'']difuran **3f** has shown very high activity on gram-negative bacteria (*Pseudomonas aeruginosa*) while interestingly the reference compound, Streptomycin has shown zero activity on the same bacteria. This compound showed bacteria specific activity. All the other angular bisaroylbenzodifurans except **3a** have shown marginal to higher growth inhibition activity with reference to the Streptomycin.

Among all the bisaroylbenzodifurans **3a-f** tested on *Streptococcus aureus* bacteria, the compounds **3c** and **3f** have shown 40-50% higher growth inhibition

activity than the reference compound Streptomycin at both concentration levels. More than 40-50% growth inhibition was observed in the compounds **3b** and **3d** when compared to the reference compound Streptomycin against gram-positive (*Staphylococcus aureus*) bacteria at 900 μg/mL concentration.

Anti-fungal activity

All the angular bisaroylbenzodifurans **3a-f** were screened for anti-fungal activity against two plant pathogenic fungi (*Drechslera halodes* and *Fusarium oxysporum*) at 160, 320, 640, and 960 μg/mL concentrations using the glass slide humid chamber technique[16]. Compounds **3c** (88.76%), **3d** (78.89%), **3f** (90.96%) showed maximum spore germination inhibition at 960 μg/mL against *Drechslera halodes* fungi and compounds **3a** (85.21%), **3b** (71.49%), **3c** (82.28%), **3d** (81.7%), and **3f** (73.91%) showed maximum spore germination inhibition at 960 μg/mL on *Fusarium oxysporum*.

Anti-implantation activity

The compounds **3a** and **3e** were screened for anti-implantation activity on albino rats and found inactive at 10 mg/kg/rat/day.

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 C17-20-ZM-390-200 MHz spectrophotometer using TMS as an internal standard; and mass spectra on a VG 7070 H ion analyzer. The C, H and O analysis of the compounds was done on a Carlo Erba model EA 1108 CHNS-O elemental analyzer.

General procedure for phase transfer catalysis method. To a magnetically stirred solution of 2,4-diacetylresorcinol **1** (0.194 g; 0.001 mole) in 30 mL of ethylene dichloride, 30 mL of 20% aq. K_2CO_3 solution and 100 mg tetrabutyl ammonium hydrogen sulphate (TBAHS) were added. The reaction mixture was heated to 50°C and the ω-bromoacetophenone **2a** (0.398g; 0.002 mole) was added dropwise over a period of 30 min at 55-60°C and maintained for 6-8 hr. The organic layer was separated, washed with 5% NaOH solution and then with water. The resulting organic layer was dried over anhydrous sodium sulphate. The excess solvent was removed under reduced pressure and the crude product was recrystallized from methanol to afford needle shaped crystals of **3a**. The compounds **3b-f** were synthesized similarly.

General procedure for microwave irradiation. 2,4-Diacetylresorcinol **1** (0.194g; 0.001 mole) and ω-bromoacetophenone **2a** (0.398g; 0.002 mole) were dissolved in methylene chloride and doped with baked K_2CO_3 and solvent was removed *in vacuo*. The resulting mixture was irradiated in microwave oven at 300W power level for 1-3 min. After irradiation, the crude product was poured into water to remove the inorganic matter. The resultant product was crystallized from methanol to afford needle shaped crystals of **3a**.

The compounds **3b-f** were synthesized by adopting the above procedure.

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