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Design and synthesis of aroylbenzodifurans as anti-implantation agents

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Bisaroylbenzodifurans namely, 3, 5-dimethyl-2, 6-dibenzoyl-(**3a**); 2, 6-di(4-methylbenzoyl)-(**3b**); 2, 6-di(4-chlorobenzoyl)-(**3c**); 2,6-di(4-bromobenzoyl)-(**3d**); 2, 6-di-(4-nitrobenzoyl)-(**3e**); 2, 6-di-(4-phenylbenzoyl)-(**3f**) and 2, 6-di-(4-methoxybenzoyl)-(**3g**)-benzo[1,2-*b*: 5,4-*b'*] difurans have been synthesized by condensing resdiacetophenone with phenacyl bromide in (a) baked K_2CO_3-dry acetone and (b) under phase transfer catalytic conditions. A comparison has been made between the two methods. PTC procedure is observed as an effective route for the synthesis of bisaroyl benzodifurans. All the seven compounds are screened for anti-implantation activity. **3a** is found to be active in preventing implantation in albino rats at 2 mg/kg/rat/day.

Benzofurans[1], aroylbenzofurans[2] were reported as antifertility agents[3-4]. We have reported 80% anti-implantation activity of 3-methyl-5-acetyl-6-hydroxy-benzofuran[5] at 20 mg/Kg/Rat and 100% anti-implantation activity of 6 furanobenzopyrones[6-7] at 10 mg/Kg/Rat/Day.

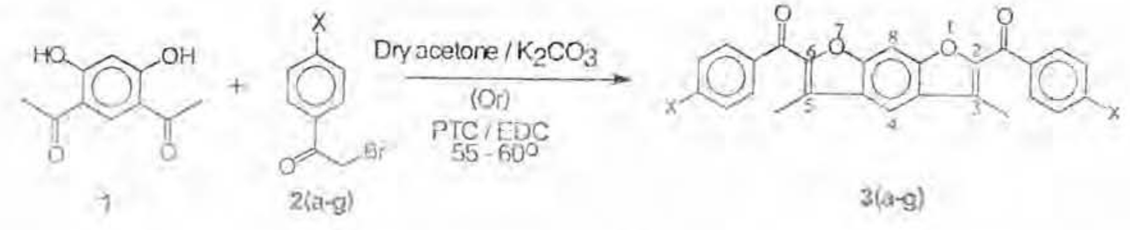
The bisaroylbenzodifurans[8] have not been reported in the literature for anti-fertility activity. Further, it was noticed that benzodifuran derivatives were endowed with activities like spasmolytic[9], vasodilatory[10] etc. Encouraged by these observations, we have designed bisaroylbenzodifuran system for anti-implantation activity. So in the present paper, the synthesis of bisaroylbenzodifurans and the anti-implantation screening results are reported.

The bisaroylbenzodifurans **3a-g** have been synthesized by condensing resdiacetophenone[11] **1** with various phenacyl bromides[12,13] **2a-g** in 1:2 mole ratio in (a) dry acetone-baked potassium carbonate for 12 hrs (method A) and (b) under phase transfer catalytic[14] conditions at 55-60° in the presence of K_2CO_3 in solvents like benzene, methylene chloride, 1, 2-dichloroethane (method B). These two methods are depicted in **Scheme I**.

A model experiment was conducted under phase transfer catalytic conditions between **1** and **2a** to ascertain the influence of (a) solvents-methylene chloride, ethylene dichloride, benzene (b) catalysts-tetrabutylammonium hydrogen sulphate (TBAHS), tetrabutylammonium bromide (TBAB), benzyl triethylammonium chloride (TEBA), cetrimide, cetyl pyridinium chloride (CpyCl) etc. and (c) temperature on the yield of benzodifuran. The results are shown in **Table I**.

Results and Discussion

In both the methods (A and B), excellent yield of benzodifuran was obtained when phenacyl bromide



Scheme I

Table I—Effect of catalyst, solvent and temperature on bisaroylbenzodifuran formation

Catalyst	Yield (%)						Reaction Period (hr)					
	EDC		MCl		Zn		EDC		MCl		Zn	
	RT	60°	RT	40°	RT	60°	RT	60°	RT	40°	RT	60°
TBAHS	65	92.7	50	70	75	85	12	4	20	15	12	6
TBAB	65	90	50	65	70	82	12.5	5	24	9	14	7
TEBA	50	70	45	60	49	68	13.5	5.5	30	9.5	15	8.5
Cetrimide	40	50	20	30	34	40	17.5	14	35	20	20	15
CpyCl	10	30	5	-	-	-	48	30	-	-	-	

EDC—1,2-Dichloroethane
MCl—Methylene chloride
Zn—Benzene
RT—Room temperature

Table II—Effect of substituents and anti-implantation activity of aroylbenzodifurans **3a-g**

Substrate	–X	Yield (%) in method		Anti-implantation activity	
		A	B	Dose : mg/Kg/Rat/Day	Activity
3a	–H	88.8	92.7	2	Active
3b	$-CH_3$	79.3	89.0	10	Inactive
3c	–Cl	82.0	85.0	20	Inactive
3d	–Br	74.3	88.6	20	Inactive
3e	$-NO_2$	71.1	84.0	10	Inactive
3f	–Ph	84.3	87.3	25	Inactive
3g	$-OCH_3$	66.1	81.3	20	Inactive

was used. The yields of benzodifurans **3d, 3f, 3g** were slightly decreased when substituted phenacyl bromides (substitution at 4-position by methoxy, bromo and phenyl groups) were used. Considerable decrease in the yield of benzodifuran **3e** was observed when 4-nitrophenacyl bromide was used. The results are shown in **Table II**.

It is evident from **Table I** that the reaction between phenacyl bromide and resdiacetophenone yields, good results with tetrabutylammonium hydrogen sulphate in ethylene dichloride at temperature 55-60°C.

The compounds were characterized by UV, IR and NMR spectral data.

The UV spectra of 3,5-dimethyl-2, 6-diaroylbenzo-[1,2-*b*:5,4-*b*′] difurans **3 a-g** displayed two absorption bands in the regions λ_{max} 322 and 358 nm as compared to the unsubstituted benzofuran[15], which showed three absorption bands at λ_{max} 245, 275 and 282 nm. It is evident that all the bands in these benzodifurans **3a-g** are observed at longer wave length regions. This bathochromic shift is due to the presence of a second furan ring and two aroyl groups, which facilitate the extended conjugation.

The IR spectra of **3a-g** showed three bands at 1600-1680 (C=O str), 1550-1590 (C=C str) and 1240-1260 cm^{-1} (C-O-C str).

In the NMR spectra of the compounds (**3a, 3b, 3c, 3e, 3f**), the methyl protons attached to the furan ring were observed as singlet at δ 2.4-2.8.

The ring closure and linear nature of the benzodifurans was confirmed by the following observations in the compounds **3a, 3b, 3c, 3e** and **3f**.

(i) The protons at C4 and C8 positions were observed as singlets at δ 7.5-8.3.

(ii) The four protons adjacent to aroyl group i.e., C 2′, 6′, 2″, 6″ were observed as doublet at δ 7.9-8.3 in the compounds **3a, 3b, 3c, 3e** and **3f**.

(iii) The protons of C 3′, 5′, 3″, 5″ were observed as doublet at δ 7.3-8.1 in the compounds **3b, 3c, 3e,** and **3f**. Whereas in **3a** one multiplet was observed at δ 7.4 -7.7 for protons of C3′, 4′, 5′, 3″, 4″, 5″ and C8.

Anti-implantation activity

All the compounds **3a-g** were tested for anti-implantation activity on albino rats between 20-2 mg/Kg/Rat/Day. Colony bred female albino rats were co-caged with coeval males of proven fertility. The day on which the vaginal smears showed the presence of spermatozoa was considered day 1 of pregnancy. The test compounds were macerated with an equal amount of gum acacia suspended in distilled water. The suspension was administered orally, over a 7-day period commencing on day 1 of pregnancy. The control rats received a mixture of gum acacia and distilled water in a similar manner. The animals were laparatomised on day 16 of pregnancy and the number of implantation sites were recorded if all the animals treated with test compound showed complete absence of implantation sites and they were considered as active. The results were given in **Table II**. Compound **3a** showed 100% anti-implantation activity at 2 mg/Kg/Rat. The substituents present at positions 4 and 4´ in compound **3a-g** showed considerable influence in decreasing the anti-implantation activity.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. The UV spectra were recorded on Shimadzu UV 160A UV-Vis-NIR spectrophotometer, IR spectra on Shimadzu FTIR model 8010 spectrophotometer and the ^{1}H NMR spectra in $CDCl_3$ on Varian C_{17}-20-ZM-390-200 MHz NMR spectrophotometer using TMS as an internal standard. The C, H, N, S and O analysis of the compounds was done on a Carlo Erba Model EA 1108 CHNS-O elemental analyser.

General procedure for the synthesis of 3,5-dimethyl-2, 6-dibenzoylbenzo [1,2-*b*:5,4-*b*′]difuran 3a

Method A. A mixture of resdiacetophenone **1** (1.94 g; 0.01 mole), ω-bromoacetophenone **2a-g** (3.98 g; 0.02 mole), baked K_2CO_3 (5g) and acetone (600 mL) was refluxed for 12 hr. The reaction mixture was cooled, excess solvent was removed and poured on to crushed ice. The solid separated was filtered, washed with water, dried and crystallized from ethanol to yield **3a-g**.

Method B. To a magnetically stirred solution of resdiacetophenone **1** (1.94 g; 0.01 mole) in 30 mL ethylene dichloride, 30 mL of 20% K_2CO_3 and 100 mg TBAHS were added. The reaction mixture was heated to 50° and the phenacyl bromide **2a-g** (0.02 mole) was added dropwise over a period of 30 min at 55-60° and maintained for 5-6 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 ethanol.

Preparation of the compounds **3b-g** was carried out by the general experimental procedure as given above.

3, 5-Dimethyl-2, 6-dibenzoylbenzo[1,2-*b*:5,4-*b*′] difuran 3a: mp 185°, yield 92.7%; UV (λ_{max}): 260, 322 and 358 nm; IR (cm^{-1}): 1640, 1560, and 1250; MS: m/z (%), M^+, 394(6), 105(56) and 77(74); ^{1}H NMR: δ 7.9-8.1(d, 4H, C2′, 6′, 2″, 6″), 7.95 (s, 1H, C4), 7.4-7.6 (m, 7H, C3′, 4′, 5′, 3″, 4″, 5″and C8) and 2.7(s, 6H, CH_3). Anal. Calc. for $C_{26}H_{18}O_4$ (394): C, 79.18; H, 4.56. Found: C, 79.12; H, 4.9%.

3, 5-Dimethyl-2, 6-di-(4-methylbenzoyl)benzo-[1, 2-*b*:5,4-*b*′]difuran 3b: mp 142°, yield 84%; UV (λ_{max}): 258 and 346 nm; IR (cm^{-1}): 1670, 1550, 1240; ^{1}H NMR: δ 8.0 (d, 4H, C2′, 6′, 2″, 6″), 7.9 (s, 1H, C4), 7.3 (d, 4H, C3′, 5′, 3″, 5″), 7.6 (s, 1H, C8) and 2.7 (s, 6H, CH_3). Anal. Calc. for $C_{28}H_{22}O_4$ (422): C, 79.62; H, 5.21. Found: C, 79.64; H, 5.23.%.

3, 5-Dimethyl-2, 6-di-(4-chlorobenzoyl)benzo-[1, 2-*b*:5,4-*b*′] difuran 3c. mp 128°, yield 85%; UV (λ_{max}): 258 and 344 nm; IR (cm^{-1}): 1680, 1590 and 1250; ^{1}H NMR: δ 8.1(d, 4H, C2′, 6′, 2″, 6″), 7.95 (s, 1H, C4), 7.45 (d, 4H, C3′, 5′, 3″, 5″), 7.6 (s, 1H, C8) and 2.7 (s, 6H, CH_3). Anal. Calc. for $C_{26}H_{16}O_4Cl_2$ (463): C, 67.39; H, 3.46. Found: C, 67.36; H, 3.48%.

3, 5-Dimethyl-2, 6-di-(4-bromobenzoyl)benzo-[1,2-*b*:5,4-*b*′]difuran 3d. mp 164°, yield 88.6%; UV (λ_{max}): 260 and 342 nm; IR (cm^{-1}): 1620, 1550, 1240; Anal. Calc. for $C_{26}H_{16}O_4Br_2$ (552): C, 56.52; H, 2.9. Found: C, 56.54; H, 2.94%.

3, 5-Dimethyl-2, 6-di-(4-nitrobenzoyl)benzo-[1,2-*b*:5,4-*b*′]difuran 3e. mp. 136°, yield 81.35%; UV (λ_{max}): 258 and 342 nm; IR (cm^{-1}): 1600, 1565, 1360 and 1250; ^{1}H NMR: δ 8.3(d, 4H, C2′, 6′, 2″, 6″), 8.3 (s, 1H, C4), 8.1 (d, 4H, C3′, 5′, 3″, 5″), 8.15 (s, 1H, C8) and 2.7(s, 6H, CH_3). Anal. Calc. for $C_{26}H_{16}O_8N_2$ (484): C, 64.46; H, 3.31; N, 5.79. Found: C, 64.42; H, 3.34; N, 5.76%.

3, 5-Dimethyl-2, 6-di-(4-phenylbenzoyl)benzo-[1,2-*b*:5,4-*b*′]difuran 3f. mp 158°, yield 87.35%; UV (λ_{max}): 262 and 346 nm; IR (cm^{-1}): 1630, 1560 and 1260; ^{1}H NMR: δ 8.25(d, 4H, C2′, 6′, 2″, 6″), 7.95 (s, 1H, C4), 7.8 (d, 4H, C3′, 5′, 3″, 5″), 7.35 (s, 1H, C8) and 2.7 (s, 6H, CH_3). Anal. Calc. for $C_{38}H_{26}O_4$ (546): C, 83.52; H, 4.76. Found: C, 83.54; H, 4.78%.

3, 5-Dimethyl-2, 6-di-(4-methoxybenzoyl)benzo-[1,2-*b*:5,4-*b′*]difuran 3g. mp 175°, yield: 89%; UV (λ_{max}): 268 and 345 nm; IR (cm^{-1}): 1642, 1570, and 1130; Anal. Calc. for $C_{28}H_{22}O_6$ (454): C, 74.01; H, 4.85. Found: C, 74.05; H, 4.82%.

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