Design and synthesis of aroylbenzodifurans as anti-implantation agents

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Bisaroylbenzodifurans namely, 3, 5-dimethyl-2, 6-dibenzyol-(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)-benzof[1,2-b:5,4-b']difurans have been synthesized by condensing resdiacetophenone with phenacyl bromide in (a) baked K₂CO₃-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 bisaryl 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, aroylbenzofurans were reported as antifertility agents. We have reported 80% anti-implantation activity of 3-methyl-5-acetyl-6-hydroxy benzofuran at 20 mg/Kg/Rat and 100% anti-implantation activity of 6-furanobenzopyrones at 10 mg/Kg/Rat/Day.

The bisaroylbenzodifurans have not been reported in the literature for anti-fertility activity. Further, it was noticed that benzodifuran derivatives were endowed with activities like spasmylytic, vasodilatory 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 with various phenacyl bromides in 1:2 mole ratio in (a) dry acetone-baked potassium carbonate for 12 hrs (method A) and (b) under phase transfer catalytic conditions at 55-60° in the presence of K₂CO₃ 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...
Table I—Effect of catalyst, solvent and temperature on bisaroylbenzodifuran formation

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>Reaction Period (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EDC</td>
<td>MCI</td>
</tr>
<tr>
<td>TBAHS</td>
<td>65</td>
<td>92.7</td>
</tr>
<tr>
<td>TBAB</td>
<td>65</td>
<td>90</td>
</tr>
<tr>
<td>TBEA</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>Cetrimide</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>CpyCl</td>
<td>10</td>
<td>30</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Substrate</th>
<th>-X</th>
<th>Yield (%) in method</th>
<th>Anti-implantation activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>Dose: mg/Kg/Rat/Day</td>
</tr>
<tr>
<td>3a</td>
<td>88.8</td>
<td>92.7</td>
<td>2</td>
</tr>
<tr>
<td>3b</td>
<td>79.3</td>
<td>89.0</td>
<td>10</td>
</tr>
<tr>
<td>3c</td>
<td>82.0</td>
<td>85.0</td>
<td>20</td>
</tr>
<tr>
<td>3d</td>
<td>74.3</td>
<td>88.6</td>
<td>20</td>
</tr>
<tr>
<td>3e</td>
<td>71.1</td>
<td>84.0</td>
<td>10</td>
</tr>
<tr>
<td>3f</td>
<td>84.3</td>
<td>87.3</td>
<td>25</td>
</tr>
<tr>
<td>3g</td>
<td>66.1</td>
<td>81.3</td>
<td>20</td>
</tr>
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</table>

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-diarylb enzofuran-1,2-b:5,4-b' diferu rans 3 a-g displayed two absorption bands in the regions 322 and 358 nm as compared to the unsubstituted benzofuran, which showed three absorption bands at 245, 275 and 282 nm. It is evident that all the bands in these benzodifurans 3a-g are observed at longer wavelength 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 8.2.4-2.8.

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 breed 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 1H NMR spectra in CDCl3 on Varian C-120-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), o-bromoacetophenone 2a-g (3.98 g; 0.02 mole), baked K2CO3 (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% K2CO3 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 (λmax): 260, 322 and 358 nm; IR (cm−1): 1640, 1560, and 1250; MS: m/z (%), 394(6), 105(56) and 77(74); 1H 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, CH3). Anal. Calc. for C26H16O4 Br2: C, 56.52; H, 2.94%.

3, 5-Dimethyl-2, 6-di-(4-chlorobenzoyl)benzo[1,2-b:5,4-b′]difuran 3c: mp 128°, yield 85%; UV (λmax): 258 and 346 nm; IR (cm−1): 1670, 1550, 1240; 1H NMR: δ 8.1 (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, CH3). Anal. Calc. for C26H16O2Cl2: C, 79.62; H, 5.21. Found: C, 79.64; H, 5.23%.

3, 5-Dimethyl-2, 6-di-(4-phenylenzoyl)benzo[1,2-b:5,4-b′]difuran 3e: mp 164°, yield 88.6%; UV (λmax): 260 and 342 nm; IR (cm−1): 1620, 1550, 1240; Anal. Calc. for C26H16O2N2: 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 3d: mp 136°, yield 81.35%; UV (λmax): 256 and 342 nm; IR (cm−1): 1600, 1565, 1360 and 1250; 1H 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, CH3). Anal. Calc. for C26H16O2N2: 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 (λmax): 262 and 346 nm; IR (cm−1): 1630, 1560 and 1260; 1H 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, CH3). Anal. Calc. for C38H24O2N2: C, 83.52; H, 4.76. Found: C, 83.54; H, 4.78%.
3, 5-Dimethyl-2, 6-di-(4-methoxybenzoyl)benzofur-an-1,2-b:5,4-b’difuran 3g. mp 175°C, yield: 89%; UV 
($\lambda_{\max}$): 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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References