Publications

1. "Regioselective Cyclodehydration of *ortho*-Hydroxy Acetyl Aryloxyketones to Benzofuran".
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2. "Studies in Synthesis of Furoflavones Possessing Anti-cancer Activity".
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4. "Studies in Synthesis and Tautomerism of New Warfarin Derivatives".
   Patel, J. M. and Soman, S. S., *communicated.*

5. "Studies in one-pot synthesis of Furoflavanones".
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Regioselective Cyclodehydration of *ortho*-Hydroxy Acetyl Aryloxyketones to Benzofuran

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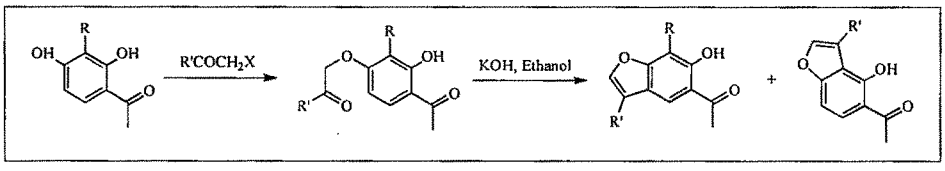

ortho-Hydroxy acetyl benzofuran derivatives have been synthesized in a regioselective cyclodehydration of aryloxyketones obtained from β-resacetophenone and α-halo ketones.

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INTRODUCTION

o-Hydroxy acetophenone are versatile building blocks serving a variety of applications such as pharmaceuticals, fine chemicals and specialty polymers. They are important starting materials in the synthesis of chalcones [1], flavonoids [2], psoralens and angelicins [3], 4-hydroxy coumarins [4], which are well known naturally occurring compounds having diverse pharmacological properties along with benzofurans [5]. Naturally occurring Pongaglabol (8-hydroxy-5-phenyl-furo[2,3-*h*]benzo[*b*]-pyran-7-one) have been synthesized from Phloroacetophenone [6]. Some bioactive compounds have been synthesized from Visnaginone (5-acetyl-6-hydroxy-4-methoxybenzo[*b*]furan) [7]. Hydroxylated benzofurans such as Euparin [8], Coumestrol [9], dehydrotremetone [10] or Cicerfuran [11] plays important role in natural defense mechanism of their plants. One pot synthesis of similar homologues has also been studied [12].

Synthesis of benzofuran based on MacLeod's work is well documented [13-16]. The synthetic pathway followed by MacLeod *et al.* has been employed to prepare the title compounds [17]; where the cyclodehydration of aryloxyketone to benzofuran has been carried out in alkaline medium instead of the generally used sulfuric acid, polyphosphoric acid, phosphorus (III) oxychloride and zinc chloride. The disadvantage with the acid catalyst is the mixture of 2- and 3-substituted benzofuran in the product by rearrangement [18]. Many instances of rearrangement leading to 2-aryl benzofuran have been observed depending on the condition (structure of ketone, medium, temperature) [19].

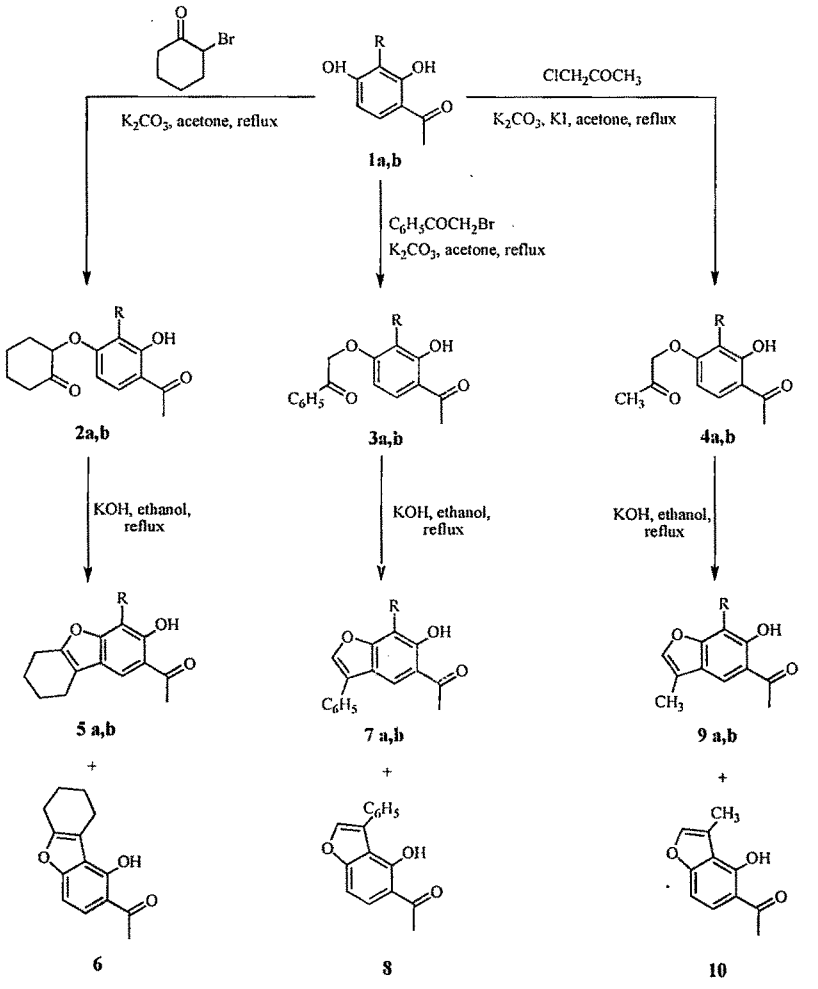
Most of the study done hitherto has been on coumarin nucleus which shows the formation of linear furocoumarin as the exclusive product with no emphasis on the formation of angular furocoumarin except as reported by A. Guiotto *et al.* using the said procedure [20]. Even K. N. Trivedi *et al.* did not report the formation of angular isomer in their synthesis of 1-(3-hydroxy-6,7,8,9-tetrahydrodibenzofuran-2-yl)-ethanone (linear isomer) [3], which now has been reported here.

In the present communication we report the regioselective cyclodehydration of aryloxyketones in an intramolecular Aldol type condensation to benzofuran derivatives. The reaction sequence for different title compounds is outlined in Scheme 1.

RESULTS AND DISCUSSION

1-(2,4-Dihydroxyphenyl)-ethanone **1a** [21], on condensation with different α-halo ketones, *e.g.* α-bromo cyclohexanone, phenacyl bromide and mono chloroacetone, in presence of anhydrous potassium carbonate/dry acetone gave 2-(4-acetyl-3-hydroxyphenoxy)-cyclohexanone **2a**, 2-(4-acetyl-3-hydroxyphenoxy)-1-phenyl-ethanone **3a** and 1-(4-acetyl-3-hydroxyphenoxy)-propan-2-one **4a** respectively. Further, 2-(4-acetyl-3-hydroxyphenoxy)-1-phenyl-ethanone **3a** when subjected to cyclization in 0.1 *N* ethanolic potassium hydroxide showed two products on tlc with very little difference in r_f values, which were then separated on column chromatography with silica gel (60-120 mesh) and petroleum ether 60-80 °C. The two products were characterized as 1-(6-hydroxy-3-phenylbenzofuran-5-yl)-ethanone **7a-linear isomer** and 1-(4-hydroxy-3-phenylbenzofuran-5-yl)-ethanone **8-angular isomer** by nmr spectra. The ^{1}H nmr showed singlets at δ 7.05 (1H, C7-H) and δ 8.13 (1H, C4-H) corresponding to the aromatic protons for linear isomer **7a** and doublets (*ortho* coupling) at δ 6.95-6.98 (1H, J = 8.8 Hz, C7-H) and δ 7.58-7.61 (1H, J = 8.8 Hz, C6-H) again corresponding to the aromatic protons for angular isomer **8**. Further, ^{13}C nmr values δ 129.179 (C-4) and δ 161.214 (C-6) for linear isomer and δ 129.306 (C-6) and δ 160.694 (C-4) for angular isomer corroborated the cyclic structure. The mechanism as established by MacLeod *et al.* is an intramolecular Aldol condensation in which the

Scheme 1



a: R=H
b: R=CH_3

phenoxide ion formed promotes attack at the exocyclic carbonyl function through the resonance stabilized carbanion generated at the position *para* relative to the phenoxide ion. The irreversibility of the process is established by abstraction of the proton from the newly formed ring junction. On acidification water is spontaneously eliminated from the labile β-hydroxy dihydrofuran ring system to give the unsaturated benzofuran. Although the carbanion generated *para* to the phenoxide ion is resonance stabilized, the formation of the carbanion generated *ortho* to the phenoxide ion cannot be ruled out as it is the basis for the formation of two isomers. The low yield of angular isomer compared to the linear isomer, which is approximately in the ratio of 1:3, is in accordance with the theory postulated above. To confirm the cyclization products and to get the higher yield of the linear isomer, we started with 1-(2,4-dihydroxy-3-methylphenyl)-ethanone **1b**, which gave the expected results.

Similar observations were recorded for the cyclization of 2-(4-acetyl-3-hydroxyphenoxy)-cyclohexanone **2a** and 1-(4-acetyl-3-hydroxyphenoxy)-propan-2-one **4a**. Potassium carbonate and triethylamine in place of potassium hydroxide failed to improve the overall yield of the cyclization reaction. Cyclization, especially in case of phenacyl bromide took more time comparatively, because of the stabilization of exocyclic carbonyl function by the phenyl ring. The structures of the compounds have been established on the basis of their elemental analyses and spectral (ir and nmr) data as shown in Table 1. The long range coupling between C3 – CH_3 and C2 – H in compounds **9a**, **9b** and **10** have been confirmed by ^1H – COSY spectra.

Table 1
Characterization Data

Compound	Mp	Yield %	Anal. Calcd.	ir (KBr): ν_{max}, cm^{-1}	nmr (ppm)
2-(4-acetyl-3-hydroxyphenoxy)-cyclohexanone **2a**	136°C lit. [3] 136°C	45.3%	$C_{14}H_{16}O_4$ (248.27): %C 67.72, %H 6.49; Found %C 68.02, %H 6.34	3468, 3128, 1788, 1699, 1605, 1211, 1256, 1177	^{1}H nmr (90 MHz, CDCl3): δ 2.51 (s, 3H, C4-$COCH_3$), 1.72-2.7 (m, 8H, -CH_2-cyclohexanone), 4.77 (t, 1H, -OC*H*(CH_2)CO-), 6.23 (d, 1H, J = 9 Hz, C6-H), 7.39 (d, 1H, J = 9 Hz, C5-H), 12.61 (s, 1H, C3-OH chelated)
2-(4-acetyl-3-hydroxy-2-methyl-phenoxy)-cyclohexanone **2b**	125°C lit. [3] 125°C	60%	$C_{15}H_{18}O_4$ (262.30): %C 68.68, %H 6.91; Found %C 68.44, %H 6.79	3379, 3098, 1734, 1632, 1611, 1259, 1223, 1149	^{1}H nmr (90 MHz, $CDCl_3$): δ 2.2 (s, 3H, C2-CH_3), 2.55 (s, 3H, C4-$COCH_3$), 1.7-2.6 (m, 8H, -CH_2-cyclohexanone), 4.7 (t, 1H, -OC*H*(CH_2)CO-), 6.2 (d, 1H, J = 9 Hz, C6-H), 7.45 (d, 1H, J = 9 Hz, C5-H), 12.72 (s, 1H, C3-OH chelated)
2-(4-acetyl-3-hydroxyphenoxy)-1-phenyl-ethanone **3a**	132-133°C	52.9%	$C_{13}H_{15}O_4$ (270.28): %C 71.10, %H 5.22; Found %C 70.86, %H 5.09	3630, 3209, 2923, 1701, 1685, 1654, 1610, 1543, 1353, 1222, 726	^{1}H nmr ($CDCl_3$): δ 2.53 (s, 3H, C4-$COCH_3$-), 5.33 (s, 2H, -OCH_2CO-), 6.4 (d, 1H, J = 2.4 Hz, C2-H), 6.5-6.6 (dd, 1H, J_{meta} = 2.42 Hz, J_{ortho} = 8.9 Hz, C6-H), 7.45-7.57 (m, 2H, C3'-H and C5'-H), 7.52-7.56 (d, 1H, J = 8.89 Hz, C5-H), 7.62-7.68 (m, 1H, C4'-H), 7.9-8 (m, 2H, C2'-H and C6'-H), 12.68 (s, 1H, C3-OH chelated)
2-(4-acetyl-3-hydroxy-2-methyl-phenoxy)-1-phenyl-ethanone **3b**	124-125°C	56%	$C_{14}H_{17}O_4$ (284.30): %C 71.81, %H 5.67; Found %C 71.86, %H 5.36	3397, 3065, 2923, 1708, 1636, 1604, 1501, 1449, 1436, 1373, 1274, 1225, 1139, 764	^{1}H nmr ($CDCl_3$): δ 2.17 (s, 3H, C2-CH3), 2.53 (s, 3H, C4-$COCH_3$), 5.35 (s, 2H, -OCH_2CO-), 6.28-6.31 (d, 1H, J = 8.9 Hz, C6-H), 7.48-7.53 (m, 2H, J_{ortho} = 7.43 Hz, C3'-H and C5'-H), 7.51-7.54 (d, 1H, J = 8.93 Hz, C5-H), 7.60-7.65 (m, 1H, J_{ortho} = 7.39 Hz, J_{meta} = 2.05 Hz, C4'-H), 7.97-8.01 (m, 2H, J_{ortho} = 7.48 Hz, J_{meta} = 1.41Hz, C2'-H and C6'-H), 12.76 (s, 1H, C3-OH chelated)
1-(4-acetyl-3-hydroxyphenoxy)-propan-2-one **4a**	102-103°C	74.53%	$C_{11}H_{12}O_4$ (208.21): %C 63.45, %H 5.80; Found %C 63.19, %H 5.61	3438, 3081, 2913, 1730, 1686, 1611, 1508, 1431, 1371, 1258	^{1}H nmr ($CDCl_3$): δ 2.27 (s, 3H, -$COCH_3$), 2.56 (s, 3H, C4-$COCH_3$), 4.59 (s, 2H, -OCH_2CO-), 6.34 (d, 1H, J = 2.44 Hz, C2-H), 6.47 (dd, 1H, J_{meta} = 2.49 Hz, J_{ortho} = 8.92 Hz, C6-H), 7.66 (d, 1H, J = 8.92 Hz, C5-H), 12.69 (s, 1H, C3-OH chelated)
1-(4-acetyl-3-hydroxy-2-methyl-phenoxy)-propan-2-one **4b**	126-128°C	79%	$C_{12}H_{14}O_4$ (222.23): %C 64.85, %H 6.34; Found %C 65.20, %H 6.31	3417, 2928, 2902, 1718, 1626, 1498, 1417, 1360, 1282, 1227, 1135, 1112	^{1}H nmr ($CDCl_3$): δ 2.18 (s, 3H, C2-CH_3), 2.31 (s, 3H, -$COCH_3$), 2.56 (s, 3H, C4-$COCH_3$), 4.60 (s, 2H, -OCH_2CO-), 6.25 (d, 1H, J = 8.97 Hz, C6-H), 7.57 (d, 1H, J = 8.94 Hz, C5-H), 12.77 (s, 1H, C3-OH chelated)
1-(3-hydroxy-6,7,8,9-tetrahydro-dibenzofuran-2-yl)-ethanone **5a-linear isomer**	186-188°C lit. [3] 182°C	64.43%	$C_{14}H_{14}O_3$ (230.26): %C 73.02, %H 6.12; Found %C 73.26, %H 6.45	3448, 2930, 1638, 1616, 1458, 1143	^{1}H nmr (90 MHz, $CDCl_3$): δ 1.6-2.0 (m, 4H, C7-CH_2- and C8-CH_2-), 2.6 (s, 3H, C2-$COCH_3$), 2.4-2.8 (m, 4H, C6-CH_2- and C9-CH_2-), 6.9 (s, 1H, C4-H), 7.7 (s, 1H, C1-H), 12.0 (s, 1H, C3-OH chelated)
1-(3-hydroxy-4-methyl-6,7,8,9-tetrahydrodibenzofuran-2-yl)-ethanone **5b**	148°C lit. [3] 148°C	49.02%	$C_{15}H_{16}O_3$ (244.28): %C 73.75, %H 6.60; Found %C 73.56, %H 6.39	3458, 2923, 1649, 1613, 1467, 1136	^{1}H nmr (90 MHz, $CDCl_3$): δ 1.7-2.0 (m, 4H, C7-CH_2- and C8-CH_2-), 2.45 (s, 3H, C4-CH_3), 2.7 (s, 3H, C2-$COCH_3$), 2.5-2.8 (m, 4H, C6-CH_2- and C9-CH_2-), 7.5 (s, 1H, C1-H), 12.60 (s, 1H, C3-OH chelated)
1-(1-hydroxy-6,7,8,9-tetrahydro-dibenzofuran-2-yl)-ethanone **6-angular isomer**	107-108°C	26.84%	$C_{14}H_{14}O_3$ (230.26): %C 73.02, %H 6.12; Found %C 73.26, %H 6.45	3568, 2938, 1635, 1616, 1560, 1462, 1438, 1317, 1065, 781	^{1}H nmr ($CDCl_3$): δ 1.77-1.94 (m, 4H, C7-CH_2- and C8-CH_2-), 2.61 (s, 3H, C2-$COCH_3$), 2.66-2.88 (m, 4H, C6-CH_2- and C9-CH_2-), 6.87-6.90 (d, 1H, J = 8.76 Hz, C4-H), 7.49-7.52 (d, 1H, J = 8.79 Hz, C3-H), 13.04 (s, 1H, C1-OH chelated)
1-(6-hydroxy-3-phenylbenzo-furan-5-yl)-ethanone **7a-linear isomer**	111-113°C	23.57%	$C_{16}H_{12}O_3$ (252.26): %C 76.17, %H 4.79; Found %C 75.86, %H 4.67	3506, 3105, 1637, 1615, 1584, 1461, 1371, 1329, 1252, 1165, 766	^{1}H nmr ($CDCl_3$): δ 2.69 (s, 3H, C5-$COCH_3$), 7.05 (s, 1H, C7-H), 7.39-7.43 (m, 1H, C4'-H), 7.48-7.52 (m, 2H, C3'-H and C5'-H), 7.57-7.60 (m, 2H, C2'-H and C6'-H), 7.68(s, 1H, C2-H), 8.13 (s, 1H, C4-H), 12.48 (s, 1H, C6-OH chelated); ^{13}C nmr ($CDCl_3$): δ 26.785 (-$COCH_3$), 100.074 (C-3), 117.098 (C-7), 119.482 (C-3a), 122.302 (C-5), 123.160 (C-4'), 127.395 (C-3', C-5'), 127.938 (C-2', C-6'), 129.179 (C-4), 131.161 (C-1'), 141.737 (C-2), 160.292 (C-7a), 161.214 (C-6), 204.040 (>C=O)
1-(6-hydroxy-7-methyl-3-phenyl-benzofuran-5-yl)-ethanone **7b**	150-151°C	65.7%	$C_{17}H_{14}O_3$ (266.29): %C 76.67, %H 5.29; Found %C 76.58, %H 5.09	3448, 3107, 3056, 2925, 1632, 1585, 1423, 1374, 1329, 1261, 1104, 770	^{1}H nmr ($CDCl_3$): δ 2.38 (s, 3H, C7-CH_3), 2.65 (s, 3H, C5-$COCH_3$), 7.36-7.41 (m, 1H, C4'-H), 7.45-7.50 (m, 2H, C3'-H and C5'-H), 7.55-7.59 (m, 2H, C2'-H and C6'-H), 7.68 (s, 1H, C2-H), 7.97 (s, 1H, C4-H), 12.68 (s, 1H, C6-OH chelated)
1-(4-hydroxy-3-phenylbenzo-furan-5-yl)-ethanone **8-angular isomer**	102-104°C	9.21%	$C_{16}H_{12}O_3$ (252.26): %C 76.17, %H 4.79; Found %C 75.86, %H 4.67	3568, 3128, 3099, 1615, 1490, 1475, 1370, 1268, 1050, 760	^{1}H nmr ($CDCl_3$): δ 2.57 (s, 3H, C5-$COCH_3$), 6.95-6.98 (d, 1H, J = 8.85 Hz, C7-H), 7.33-7.37 (m, 1H, C4'-H), 7.40-7.42 (m, 2H, C3'-H and C5'-H), 7.53 (s, 1H, C2-H), 7.58-7.61(d, 1H, J = 8.88 Hz, C6-H), 7.64-7.66 (m, 2H, C2'-H and C6'-H), 13.60 (s, 1H, C4-OH chelated); ^{13}C nmr ($CDCl_3$): δ 26.922 (-$COCH_3$), 103.787 (C-3), 114.363 (C-7), 115.521 (C-3a), 124.013 (C-5), 127.465 (C-4'), 127.647 (C-3', C-5'), 128.089 (C-2', C-6'), 129.306 (C-6), 131.024 (C-1'), 141.495 (C-2), 160.106 (C-7a), 160.694 (C-4), 204.188 (>C=O)

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