HETEROCYCLES FROM DIACETYL PHENOLS: SYNTHESIS OF BENZODIPYRANS, ACETYLCHROMENES AND PYRANO[1,2]BENZISOXAZOLES§

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Abstract- Novel and facile syntheses of benzodipyrans, acetylchromenes and pyranol[1,2]benzisoxazoles from 2,4- and 4,6-diacetylresorcinols have been described. Regioselective condensations and reductions have been used as the key steps.

Condensations between the enolates of appropriate o-hydroxyacetophenones generated under equilibrium conditions by conventional bases, with electrophilic carbons of ketones, aldehydes and esters have been used in the synthesis of oxygen heterocycles[1]. However, each of them suffers from one shortcoming or the other. We have shown that kinetically generated enolates of o-hydroxyacetophenones produced by using strong bases of low nucleophilicity undergo smooth condensations with a variety of electrophiles under mild experimental conditions and in high yields. This strategy has been utilized successfully in the syntheses of different classes of oxygen heterocycles such as 4-chromanones[2], 2H-chrom-3-enes[3], flavones[4], chromones[5] and crotonophenones[6]. The scope of this methodology was further extended by the synthesis of more complex oxygen heterocycles such as pyranoflavones[7], pyranochromones[5], cannabinoid synthon[8] and 3-prenylated flavones[9]. Mild experimental conditions and its amenability to small scale preparations make this methodology particularly suitable for the synthesis of isotopically labelled compounds as exemplified by the syntheses of [^{3}H]-precocenes[10]. In continuation of this work the synthetic utility of appropriately substituted polyacetylphenols has been explored. These substrates contain more than one reactive site which in principle can be used for the construction of one or more heterocyclic rings within the same molecule.

Photochromic[11] and biological properties[12] of chromenes (benzopyrans) prompted us to undertake sysnthesis of different variations of chromeno compounds. Earlier we have described the synthesis of 2,2-dimethylchromenes[3] and several chromeno compounds fused with different heterocycles[5,7].

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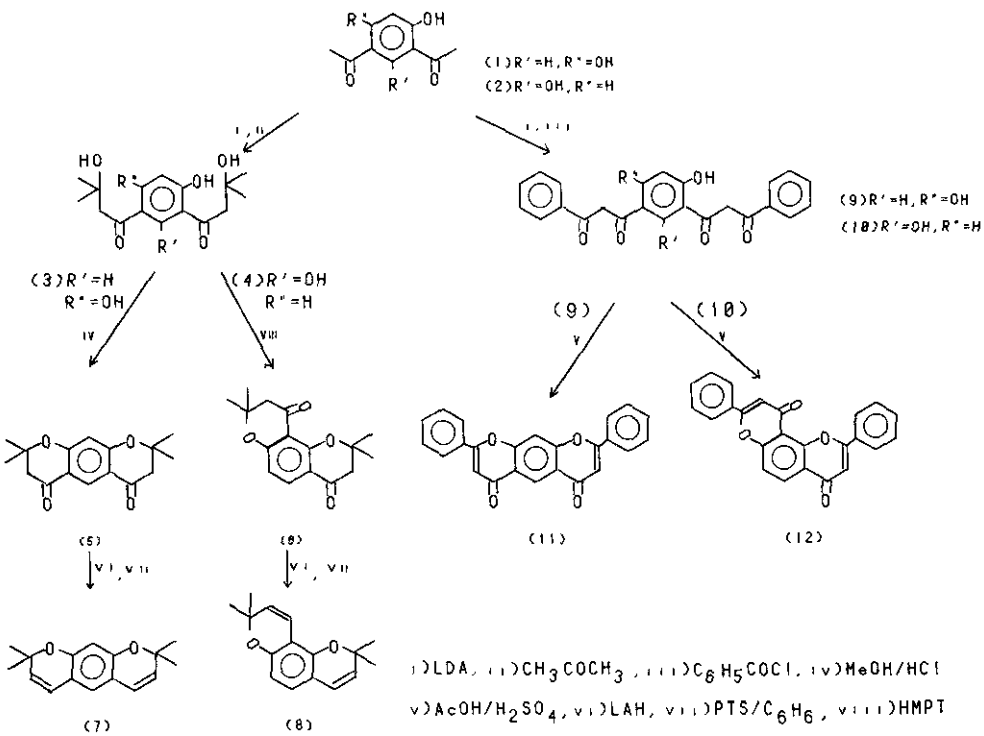
§ Dedicated to Professor Sir Derek Barton on the occasion of his 70th birthday.

In this communication the use of diacetylresorcinols (1) and (2) in the synthesis of benzodipyrans, acetylchromenes and pyrano[1,2]benzisoxazoles has been summarised.

Condensation at both the sites:

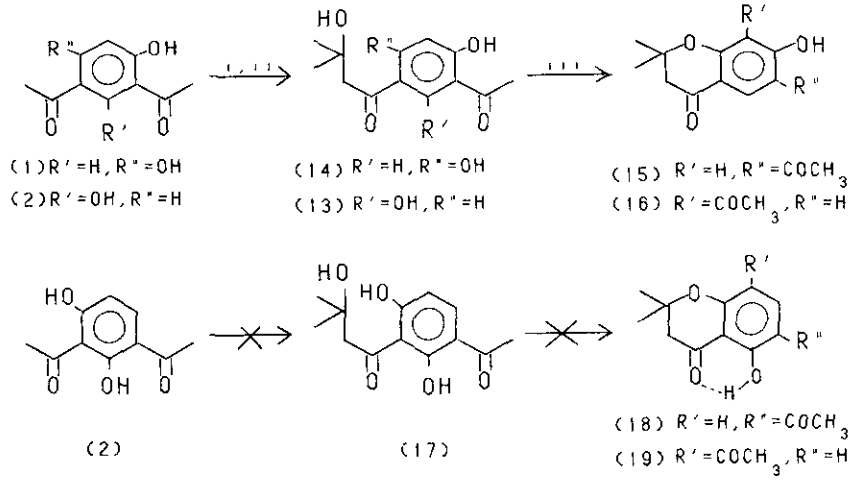
Enolates from 4,6- and 2,4-diacetylresorcinols (1 and 2 respectively) generated by deprotonation using lithium diisopropylamide (LDA) at -25°C underwent condensation with two equivalents of acetone to give bis-ß-ketols (3) and (4) at -40°C and 0°C respectively. Compound 3 was cyclised (MeOH/HCl[5]) to dichromanone (5). Reduction of 5 followed by dehydration gave dichromene (7) in satisfactory yield[13]. Cyclisation of 4 with MeOH/HCl gave poor yield of dichromanone (6) but its yield could be improved to 74% when cyclodehydration was carried out by the recently described method using HMPT[8]. Angularly fused dichromene (8) was obtained from 6 by the same sequence of reactions as described for 5[13]. The dichromenes 7 and 8 are reported to have anti-juvenile hormone activity[14]. Condensation of enolates of 1 and 2 with benzoyl chloride and cyclodehydration of the resultant bis-ß-diketones 9 and 10 gave diflavones 11 and 12[13]. No O-aroylation was observed under the experimental conditions employed[5].



Selective condensations:

The synthetic utility of 1 and 2 could be augmented by carrying out regioselective condensations at one of the two electrophilic sites so that the other is available for further elaboration by synthetic procedures.

2,2-Dimethyl-8-acetyl-7-hydroxy-4-chromanone (16): Good yield of ß-ketol (13) was obtained by the reaction of 2 with four equivalents of LDA followed by addition of acetone at -40°C (70%, mp 74-75°C); ir ($CHCl_3$): 3450, 1610, 1620 cm^{-1}; ^1H nmr (60 MHz,$CDCl)_3$) δ:1.38 (s, 6H), 2.78 (s, 3H), 3.10 (s, 2H), 6.45 (d, 1H, J=9Hz), 7.84 (d, 1H, J=9Hz), 14.30 (s, 1H), 14.69 (s, 1H). Ms (m/z): 252 (M^+). The alternative structure 17 for the ß-ketol was ruled out on the following grounds: The ß-ketol on cyclodehydration with HMPT (150°C, 2 h) gave a hydroxyacetylchromanone (89%, mp 110-111°C)[8]. Ir ($CHCl_3$): 1687 and 1630 cm^{-1} (chromanone and chelated acetyl groups respectively). ^1H Nmr (60 MHz, $CDCl_3$) δ: 1.58 (s, 6H), 2.74 (s, 5H), 6.50 (d, 1H, J=9 Hz), 8.00 (d, 1H, J=9 Hz), 14.05 (s, 1H). Ms (m/z): 234 (M^+). The presence of ir absorption at 1687 cm^{-1} for a non-hydrogen bonded carbonyl at position-4 of chromanone[15] and a strongly hydrogen bonded acetyl carbonyl absorption at 1630 cm^{-1} favour the structure 16 for the cyclised product. The alternate structure 17 for the ß-ketol would have given the compounds 18 and/or 19, both of which contain strongly hydrogen bonded 4-carbonyl groups. Unequivocal proof for the structures 16 for the chromanone and 13 for the ß-ketol, was obtained by conversion of 16 to known compound (24) as described later. This established the regiospecificity of the condensation of acetone with the acetyl carbonyl group of 2.



2,2-Dimethyl-6-acetyl-7-hydroxy-4-chromanone (15): Attempts were also made to affect selective condensation at one of the two acetyl groups of 1. As compared to 2 the equivalency of hydroxyls at 1 and 3 positions and acetyl groups at 4 and 6 positions in 1 is evident from the spectral data [1: ^{1}H nmr ($CDCl_3$, 60 MHz) δ: 2.63 (s, 6H, 2 X CH_3), 6.43 (s, 1H, 2-H), 8.21 (s, 1H, 5-H), 12.90 (s, 2 X OH); ^{13}C nmr ($CDCl_3$, 125 MHz) δ: 163.7 (C-1 and C-3), 104.7 (C-2), 135.8 (C-4 and C-6), 25.56 (2 X CH_3), 204.7 (2 X >CO)] made selective condensation difficult. After much experimentation, optimum regioselectivity was obtained when the base (LDA or LiHMDS, 3 equivalents) was added (i.e. inverse addition) to the solution of 1 in THF at -50°C followed by addition of acetone at the same temperature. The condensation product (14) was obtained in 65% yield, mp 84°C; ir ($CHCl_3$): 3450, 1660, 1640 cm^{-1}; ^{1}H nmr (60 MHz, $CDCl_3$) δ: 1.44 (s, 6H), 2.67 (s, 3H), 3.16 (s, 2H), 6.46 (s, 1H), 8.32 (s, 1H), 12.79 (s, 1H), 12.89 (s, 1H). Ms (m/z): 252 (M^+). 14 was converted *to 15 by heating with HMPT*[8] *(91%, mp 120-121°C). Ir ($CHCl_3$): 1700, 1640 cm^{-1}; ^{1}H nmr* (60 MHz, $CDCl_3$) δ: 1.50 (s, 6H), 2.60 (s, 3H), 2.70 (s, 2H), 6.39 (s, 1H), 8.39 (s, 1H), 12.59 (s, 2H). Ms (m/z): 234 (M^+). The assignments of the structures 15 and 16 are fully in agreement with their spectral and microanalytical data[16].

Compounds 15 and 16 are important synthons because they have o-hydroxyacetyl system which can be elaborated further.

Selective reductions:

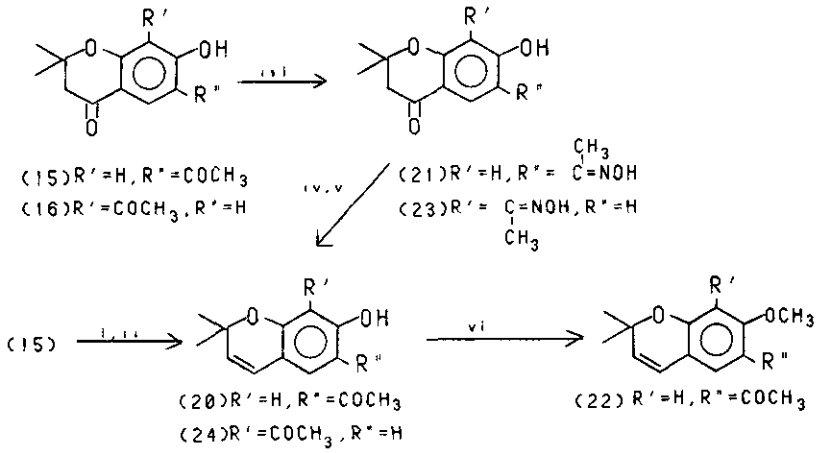
Chromenes (benzopyrans) with an acetyl group para to heterocyclic oxygen occur widely in the family, Asteraceae[12]. Several syntheses of acetylchromenes have been described[17]. In an improved synthesis we have made use of selective reduction at 4-carbonyl of acetylchromanones by a) Meerwein-Ponndorf-Verley (MPV) reduction and b) Selective protection of acetyl carbonyl group by oximation.

a) MPV reduction: It has been reported that non-chelated carbonyl groups can be reduced preferentially to chelated ones by MPV reduction[18]. We have utilized the selectivity by the preferential reduction of 4-carbonyl function of 15 employing aluminium iso-propoxide in iso-propanol. The dehydration of the reduced product gave 2,2-dimethyl-6-acetyl-7-hydroxychromene (20) in 38% yield. 20 *was identical to eupatoriochromene isolated from* Eupatorium riparium Regel[19]. Earlier, 20 was synthesised in poor yield from resacetophenone by prenylation followed by cyclisation and dehydrogenation[17].

b) via Selective oximation: A simple and effective method for protection of the carbonyl function can be through selective oximation. It has been reported that a hydrogen bonded carbonyl function can be oximated preferentially to a non-chelated one[20]. Thus monoxime (21) was prepared by stirring 15 with an equivalent amount of NH_2OH/HCl in the presence of NaOAc in ethanol at room

temperature (88%, mp 276°C decomp.). The singlet at 2.69 (2H) in ^{1}H nmr spectrum for the 3-methylene group and a strong ir absorption at 1680 cm^{-1} suggested that carbonyl of chromanone is intact and therefore oximation must have taken place at the acetyl carbonyl. The other data ^{1}H nmr (60 MHz, $CDCl_3$) δ: 1.42 (s, 6H), 2.36 (s, 3H), 2.69 (s, 2H), 6.40 (s, 1H), 8.00 (s, 1H); ms (m/z): 249 (M^+) is also in agreement with the assigned structure 21 for the monoxime. The reduction at C-4 carbonyl function was carried out using $NaBH_4$ in ethanol at room temperature. Treatment of the reduced product with acidic $TiCl_3$[21] brought about deoximation and dehydration in one step giving 20 in 60% yield. Methylation of 20 was carried out at room temperature by ultrasound irradiation[22] of a mixture of 20, methyl iodide and K_2CO_3 in acetone. Methylated product 22 was identical with encecalin, an insecticidal and antifeedant principle isolated from Encelia californica[23].

Selective oximation of 16 gave a monoxime (23) in excellent yield (83%, mp 192°C). The structure for the monoxime was supported by physical and chemical data. Ir ($CHCl_3$): 1660, 1620, 1590 cm^{-1}; ^{1}H nmr (60 MHz, $CDCl_3$) δ: 1.52 (s, 6H), 2.36 (s, 3H), 2.72 (s, 2H), 6.50 (d, 1H, J=9 Hz), 7.76 (d, 1H, J=9 Hz). Ms (m/z): 249 (M^+). However reduction of the carbonyl group followed by dehydration and deoximation gave poor yield of 2,2-dimethyl-8-acetyl-7-hydroxychromene (24). Identity of 24 was established by comparison of spectral data and chemical properties with those reported in the literature[24].



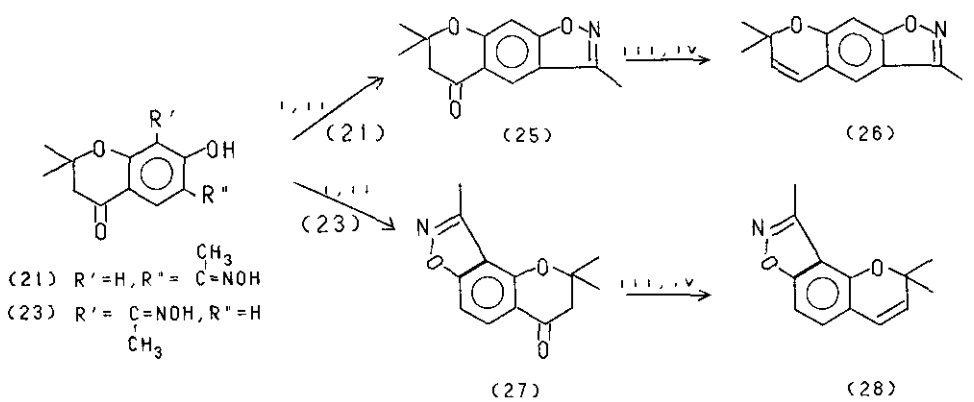
i)MPV, ii)PTS/C_6H_6, iii)NH_2OH/NaOAc, iv)$NaBH_4$; v)$TiCl_3/H^+$, vi)CH_3I, (

Pyrano[1,2]benzisoxazoles:

In view of biological properties of chromenes such as phototoxicity[25], anti-microbial[12], anti-juvenile *hormone*[26], *anti-tumor*[27], insecticidal[12] and antifeedant activities[28], it was of interest to synthesise chromeno compounds fused with other heterocycles. Isoxazoles are known to impart biological activities to various classes of compounds[29]. *In our efforts* towards the synthesis of new bioactive heterocycles, we were interested in developing a route to pyranobenzisoxazoles. In our work, thermal decomposition of o-hydroxyarylketoxime acetate[30] was used for the formation of benzisoxazole ring; pyran ring was constructed around o-hydroxyacetyl by condensation with acetone.

3,7,7-Trimethyl-7H-pyrano[3,2-f]-1,2-benzisoxazole (26): o-Hydroxyketoxime functionality of 21 was conveniently converted to isoxazole (25) by acetylation followed by thermal cyclisation. Reduction of 25 with $NaBH_4$ to corresponding 4-ol followed by p-toluenesulphonic acid catalysed dehydration gave 26 (70%, *mp* 82°C). ^1H Nmr (60 MHz, CCl_4) δ: 1.46 (s, 6H), 2.49 (s, 3H), 5.69 (d, 1H, J=9 Hz), 6.44 (d, 1H, J=9 Hz), 6.92 (s, 1H), 7.16 (s, 1H); ir ($CHCl_3$): 1620, 1580, 1540, 1220 cm^{-1}. Uv (MeOH) λ max: 239, 285 nm. Ms (m/z): 215 (M^+).

2,2,9-Trimethyl-2H-pyrano[2,3-e]-1,2-benzisoxazole (28): The monoxime 23 was converted to 27 (94%) as described earlier. Reduction of 27 followed by dehydration gave 28 (89%, *mp* 77°C); ^1H *nmr* (500 MHz, CCl_4) δ: 1.41 (s, 6H), 2.54 (s, 3H), 5.40 (d, 1H, J=10 Hz), 6.26 (d, 1H, J=10 Hz), 6.84 (d, 1H, J=9 Hz), 6.99 (d, 1H, J=8 Hz); ir ($CHCl_3$): 1650, 1630, 1600, 1250 cm^{-1}. Uv (MeOH) λ max: 235 nm. Ms (m/z): 215 (M^+).



i) Ac_2O, ii) Δ, iii) $NaBH_4$, iv) PTS/C_6H_6

Thus, the synthetic potential of diacetylresorcinols using regioselective reactions has been exemplified by the preparation of several heterocycles including mixed heterocyclic systems. We believe that this synthetic strategy has wider application and can be used for the synthesis of a variety of heterocycles using easily accessible polyacetylated polyphenols.

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