A Convenient One-pot Synthesis of New 3-(4-Aryl-5-oxo-5,6,7,8-tetrahydro-*4H*-chromen-2-yl)-2*H*-chromen-2-ones

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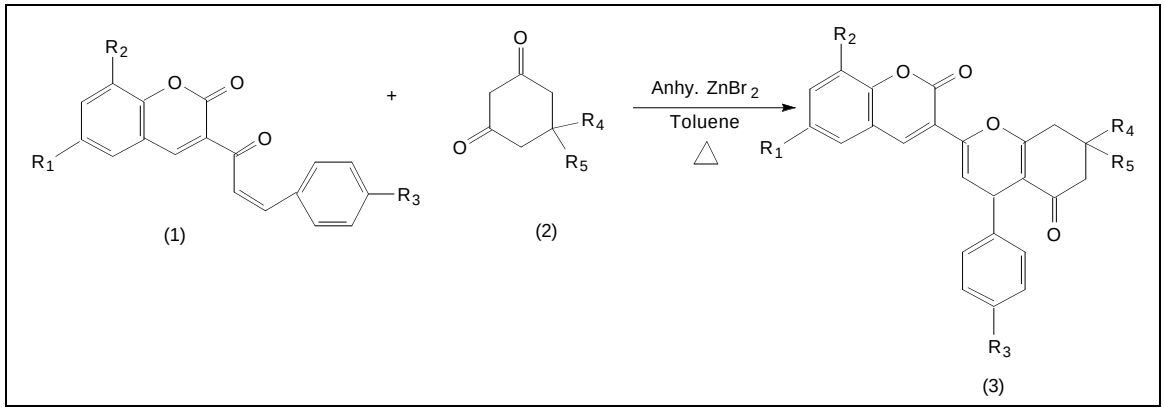

Anhydrous zinc bromide catalysed reactions of arylidine-3-acetyl coumarins (**1a-c**) and 5,6-benzoanalogs of arylidine 3-acetyl coumarins (**4a,4b**) with 1,3-cyclohexanedione gives 3-(4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromen-2yl)-2*H*-chromen-2-ones (**3a, 3c**) and 5,6-benzoanalogs of 3-(4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromen-2yl)-2*H*-chromen-2-one (**5a,5b**). Under similar conditions arylidine-3-acetylcoumarins (**1a, 1b,1d, 1e, 1f**) and 5,6-benzoanalog of arylidine 3-acetyl coumarin (**4b**) react with 5,5-dimethyl-1,3-cyclohexanedione (dimedone) yielding 3-(4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromen-2-yl)-*2H*-chromen-2-ones (**3d-3h**) and the 5,6-benzoanalog of 3-(4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-*4H*-chromen-2-yl)-*2H*-chromen-2-one (**5c**).

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INTRODUCTION

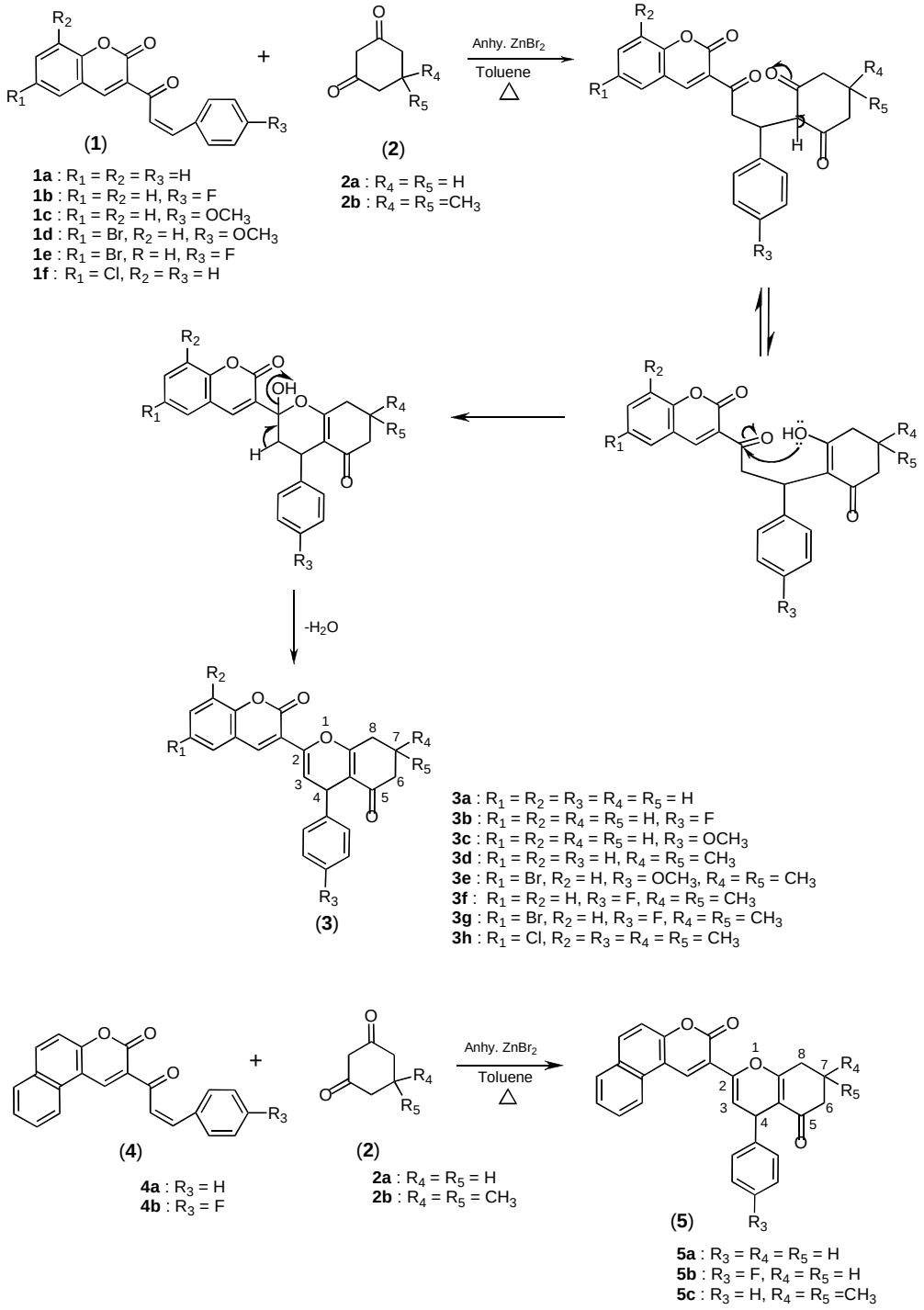
There is a continuous interest in the synthesis of benzopyrans, since they possess antijuvenile hormone activity [1], antianaphylactic activity in trachea [2] and are found to be antiallergic [3,4], antinflammatory [5], and anticancer [6] agents and also helpful in diabetic complications [7]. In continuation of our earlier work [8-10] on the synthesis of benzopyrans, we report here a new one step efficient synthesis of 3-(4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromen-2yl)-2*H*-chromen-2-ones in good yields (65-78%).

The synthesis utilizes the condensation of cyclohexane-1,3-dione and 5,5-dimethyl-1,3-cyclohexanedione with different chalcones (**1a-1f**) derived from 3-acetyl coumarins and the corresponding 5,6-benzo derivatives (**4a-c**) of 3-acetyl coumarins.

The formation of these compounds (**3-5**) may be explained by the initial formation of a 1:1 adduct which presumably underwent cyclisation in the presence of $ZnBr_2$ catalyst as shown in Scheme-1. The Lewis acid, zinc bromide will effectively polarize the carbon-oxygen double bond by coordinating the oxygen to the electron deficient Zn in $ZnBr_2$. Due to this carbonyl carbon will become more positively charged and is easily attacked by nucleophillic enolic hydroxy group to give the cyclised compound **3** and **5**. During the above reaction there is no formation of Micheal adducts between cyclic 1,3-diketones and chalcones. This is confirmed from analytical and spectral data.

The infrared spectra of the newly prepared chromen derivatives (**3-5**) are consistent with their structures. They exhibit strong carbonyl bands at 1717-1741 cm^{-1} for lactone and 1656-1670 cm^{-1} for ketone respectively. The C-O stretching is observed at 1205-1213 cm^{-1}. The ^1H nmr spectrum of **3a** exhibited besides the usual signals, two characteristic doublets at δ 4.47 (1H, J = 6 Hz, C_4-H) and at δ 6.66 (1H, J = 3 Hz, C_3-H). Its mass spectrum gave a peak at m/z 370 (M^+). The ^1H nmr spectrum of **3d** showed besides usual signals, the protons at C_6 as an AB quartet at δ 2.14 – 2.33. The appearance of AB quartet clearly showed that two methylene protons are non equivalent or not identical. The aniosotropic effect of the adjacent carbonyl is responsible for their difference. The protons of C_4 and C_5 have appeared as doublets at δ 4.45 (d, 1H, J = 6 Hz, C_4-H) and 6.66 (d, 1H, J = 6 Hz, C_5-H).

Scheme-1



The ^{13}C nmr spectrum of **3d** showed two different signals for gemdimethyls at δ 28.0 and 29.4 respectively indicating that they are in different planes. Lactone carbonyl carbon appeared at δ 165.5 and the carbonyl carbon appeared at δ 197.2. The other carbon signals appeared in the usual region.

EXPERIMENTAL

General. Melting points were determined by POLMAN melting point apparatus (Model No. MP-96) and are uncorrected. The IR spectra (ν_{max} cm^{-1}) were recorded on Perkin-Elmer spectrophotomer. The ^1H nmr, ^{13}C nmr spectra were recorded on 300 MHz Bruker-Avance instrument using

TMS as an internal standard. The mass spectra were scanned on Perkin-Elmer SCIEX API-2000 instrument. The purity of all compounds was established by TLC analysis using Merck precoated silica gel $60F_{254}$ plates (0.2 mm thickness).

General Procedure for synthesis of 3-(4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromen-2-yl)-2*H*-chromen-2-ones (3a-g and 5a-c). Compound **1** or **4** (0.01 mole) was dissolved in Toluene (30 ml) at 25°C, compound **2** (0.01 mole) and zinc bromide (0.003 mole) were added to the solution. The resulting suspension was heated to reflux (110 °C). The byproduct, water was removed azeotropically using Dean stark apparatus. The reflux was continued till the reaction gets completed (~3 hours). Toluene was removed by distillation under reduced pressure and recrystallised the product from isopropyl alcohol.

3-(5-Oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromen-2-yl)-2*H*-chromen-2-one (3a) was obtained by the reaction of **1a** with **2a** in 70% yield, mp 238-240 °C; ir (potassium bromide): 1730 (C=O, lactone), 1656 (C=O), 1208 cm^{-1}; ^1H nmr (DMSO-d_6): 2.05 (m, 2H, CH_2), 2.34 (m, 2H, CH_2), 2.78 (m, 2H, CH_2), 4.47 (d, 1H, J = 6 Hz, C_4-H, pyran), 6.66 (d, 1H, J = 6 Hz, C_3-H, pyran), 7.19-7.72 (m, 9H, Ar-H), 8.44 (s, 1H, C_4-H of coumarin); ms: (12.5 eV, ESI) m/z 370 (molecular ion); *Anal.* Calcd. for $C_{24}H_{18}O_4$ (370.4): C, 77.83; H, 4.90. Found: C, 77.78, H, 4.80.

3-(4-(4-Fluorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromen-2-yl)-2*H*-chromen-2-one (3b) was obtained by the reaction of **1b** with **2a** in 74% yield, mp 231-233 °C; ir (potassium bromide) : 1717 (C=O, lactone), 1670 (C=O), 1208 cm^{-1}; ^1H nmr (DMSO-d_6) : 2.02 (m, 2H, CH_2), 2.32 (m, 2H, CH_2), 2.77 (m, 2H, J = 6 Hz, CH_2), 4.49 (d, 1H, J = 6 Hz, Pyran), 6.64 (d, 1H, J = 6 Hz, Pyran), 7.08 – 7.69 (m, 7H, Ar-H), 7.88 (d, 1H, Ar-H), 8.43 (s, 1H, C_4-H of coumarin); *Anal.* Calcd. for $C_{24}H_{17}FO_4$ (388.39): C, 74.22; H, 4.41. Found: C, 74.15; H, 4.38.

3-(4-(4-Methoxyphenyl)-5-oxo-5,6,7,8-Tetrahydro-4*H*-chromen-2-yl)-2*H*-chromen-2-one (3c) was obtained by the reaction of **1c** with **2a** in 65% yield, mp 132-134 °C; ir (potassium bromide): 1732 (C=O, lactone), 1657 (C=O), 1280 cm^{-1}; ^1H nmr ($CDCl_3$) : 2.07 (m, 2H, CH_2), 2.38 (m, 2H, CH_2), 2.71 (m, 2H, CH_2), 3.76 (s, 3H, CH_3), 4.52 (d, 1H, J = 6 Hz, pyran), 6.82 (d, 2H, J = 9 Hz, Ar-H), 6.89 (d, 1H, J = 5.14 Hz, pyran), 7.23 (d, m, 4H, Ar-H), 7.6 – 7.66 (m, 1H, Ar-H), 7.75 (s, 1H, Ar-H), 8.47 (s, 1H, C_4-H of coumarin); *Anal.* Calcd. for $C_{25}H_{20}O_5$ (400.42): C, 74.98; H, 5.03. Found: C, 75.12; H, 4.92.

3-(7,7-Dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromen-2-yl)-2*H*-chromen-2-one (3d) was obtained by the reaction of **1a** with **2b** in 75% yield, mp 140-142 °C; ir (potassium bromide): 1738.8 (C=O, lactone), 1656 (C=O), 1207 cm^{-1}; ^1H nmr (DMSO-d_6): 1.05 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 2.16 (ABq, 2H, -$COCH_2$), 2.69 (s, 2H, CH_2), 4.45 (d, 1H, J = 6 Hz, pyran), 6.66 (d, 1H, J = 6 Hz, pyran), 7.18 – 7.85 (m, 9H, Ar-H), 8.44 (s, 1H, C_4-H of coumarin); ^{13}C nmr (DMSO-d_6) 28.0, 29.4, 32.7, 34.8, 41.2, 51.0, 111.9, 115.8, 116.1, 116.7, 118.7, 119.5, 125.7, 130.0, 130.3, 130.4, 133.4, 139.4, 141.4, 141.9, 153.4, 158.3, 160.1, 163.3, 165.5, 197.2; ms: m/z 398 (molecular ion); *Anal.* Calcd. for $C_{26}H_{22}O_4$ (398.45): C, 78.37; H, 5.56. Found: C, 78.28; H, 5.46.

6-Bromo-3-(4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromen-2-yl)-2*H*-chromen-2-one (3e) was obtained by the reaction of **1d** with **2b** in 72% yield, mp 178-180 °C; ir (potassium bromide) : 1741 (C=O, lactone), 1656 (C=O), 1205 cm^{-1}; ^1H nmr (DMSO-d_6): 1.04 (s, 3H, CH_2), 1.09 (s, 3H, CH_3), 2.29 (ABq, 2H, J = 18 Hz, -$COCH_2$), 2.58 (s, 2H, CH_2), 3.7 (s, 3H, OCH_3), 4.39 (d, 1H, J = 6 Hz, pyran), 6.64 (d, 1H, J = 6 Hz, Pyran), 6.85 (d, 2H, J = 6 Hz, Ar-H), 7.14 (d, 2H, J = 9Hz, Ar-H), 7.39 (d, 1H, J = 9Hz, Ar-H), 7.78 (d, 1H, J = 9 Hz, Ar-H), 8.12 (d, 1H, J = 2.1 Hz, Ar-H), 8.41 (s, 1H, C_4-H of coumarin); *Anal.* Calcd. for $C_{27}H_{23}BrO_5$ (507.37): C, 63.91; H, 4.56. Found: C, 63.69; H, 4.60.

3-(4-(4-Fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromen-2-yl)-2*H*-chromen-2-one (3f) was obtained by the reaction of **1b** with **2b** in 72% yield, mp 196-198 °C. ir (potassium bromide): 1735 (C=O, lactone), 1666 (C=O), 1209 cm^{-1}. ^1H nmr (DMSO-d_6): 1.04 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 2.22 (ABq, 2H, J = 15 Hz, $COCH_2$), 2.68 (s, 2H, CH_2), 4.48 (d, 1H, J = 6 Hz, pyran), 6.64 (d, 1H, J = 3 Hz, pyran), 7.09 – 7.68 (m, 7H, Ar-H), 7.87 (d, 1H, J = 6 Hz, Ar-H), 8.45 (s, 1H, C_4-H of coumarin); *Anal.* Calcd. for $C_{26}H_{21}FO_4$ (416.44): C, 74.98; H, 5.08. Found: C, 75.11; H, 5.10.

6-Bromo-3-(4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromen-2-yl)-2*H*-chromen-2-one (3g) was obtained by the reaction of **1e** with **2b** in 76% yield, mp 175-177 °C; ir (potassium bromide): 1737 (C=O, lactone), 1661 (C=O), 1206 cm^{-1}. ^1H nmr ($CDCl_3$), 1.05 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 2.25 (ABq, 2H, J = 18 Hz, -$COCH_2$), 2.56 (s, 2H, CH_2), 4.53 (d, 1H, J = 6 Hz, pyran), 6.88 (d, 1H, J = 6 Hz, pyran), 7.19 – 7.29 (m, 4H, Ar-H), 7.59 – 7.68 (m, 3H, Ar-H), 8.41 (s, 1H, C_4-H of coumarin); *Anal.* Calcd. for $C_{26}H_{20}BrFO_4$ (495.35): C, 63.04; H, 4.07. Found: C, 63.09; H, 4.07.

6-Chloro-3-(7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromen-2-yl)-2*H*-chromen-2-one (3h) was obtained by the reaction of **1f** with **2b** in 70% yield, mp 190-192 °C; ir (potassium bromide): 1736 (C=O, lactone), 1205 cm^{-1}. ^1H nmr ($CDCl_3$): 1.09 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 2.26 (ABq, 2H, -$COCH_2$), 2.58 (s, 2H, CH_2), 4.54 (d, 1H, pyran), 6.9 (d, 1H, pyran), 7.28 – 7.64 (m, 7H, Ar-H), 8.04 (s, 1H, Ar-H), 8.42 (s, 1H, C_4-H of coumarin); *Anal.* Calcd. for $C_{26}H_{21}ClO_4$ (432.91): C, 72.14; H, 4.89. Found: C, 72.20; H, 4.81.

2-(5-Oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromen-2-yl)-3*H*-benzo[*f*]chromen-3-one (5a) was obtained by the reaction of **4a** with **2a** in 65% yield, mp 246-248 °C; ir (potassium bromide): 1730 (C=O, lactone), 1656 (C=O), 1209 cm^{-1}; ^1H nmr ($CDCl_3$): 2.05 (m, 2H, CH_2), 2.33 (m, 2H, CH_2), 2.90 (m, 2H, -$COCH_2$), 4.50 (d, 1H, J = 6 Hz, Pyran), 6.72 (d, 1H, J = 6 Hz, pyran), 7.16-7.29 (m, 5H, Ar-H), 7.59 – 7.83 (m, 3H, Ar-H), 8.09 (d, 1H,J = 9 Hz, Ar-H), 8.23 (d, 1H, J = 9 Hz, Ar-H), 8.66 (d, 1H, J = 8.7 Hz, Ar-H), 9.07 (s, 1H, C_4-H of coumarin); *Anal.* Calcd. for $C_{28}H_{20}O_4$ (420.46): C, 79.98; H, 4.79. Found: C, 79.92; H, 4.70.

2-(4-(4-Fluorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromen-2-yl)-3*H*-benzo[*f*]chromen-3-one (5b) was obtained by the reaction of **4b** with **2a** in 73% yield, mp 238-240 °C; ir (potassium bromide): 1730 (C=O, lactone), 1655 (C=O), 1217 cm^{-1}; ^1H nmr ($CDCl_3$) : 2.12 (m, 2H, CH_2), 2.44 (m, 2H, CH_2), 2.84 (m, 2H, CH_2), 4.62 (d, 1H, J = 6 Hz, pyran), 6.94 (d, 1H, J = 6 Hz, pyran), 7.30 (m, 2H, Ar-H), 7.50-7.98 (m, 6H, Ar-H), 8.05 (d, 1H, Ar-H), 8.37 (d, 1H, Ar-H), 8.93 (s, 1H, C_4-H of coumarin); *Anal.* Calcd. for $C_{28}H_{19}FO_4$ (438.45): C, 76.70; H, 4.36. Found: C, 76.40, H, 4.27.

2-(7,7-Dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromen-2-yl)-3*H*-benzo[*f*]chromen-3-one (5c) was obtained by the reaction of **4a** with **2b** in 78% yield, mp 208-210°C; ir (potassium bromide): 1721 (C=O, lactone), 1655 (C=O), 1213 cm^{-1}. ^1H nmr ($CDCl_3$) : 1.13 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 2.27 (ABq, 2H, -$COCH_2$), 2.56 (s, 2H, CH_2), 4.59 (d, 1H, J = 5.4 Hz, pyran), 6.96 (d, 1H, J = 5.4 Hz, pyran), 7.26 – 7.75 (m, 7H,

Ar-H), 7.93 – 8.02 (m, 3H, Ar-H), 8.35 (d, 1H, Ar-H), 8.9 (s, 1H, C_4-H of coumarin); *Anal*. Calcd. for $C_{30}H_{24}O_4$ (448.51): C, 80.33; H, 5.39. Found: C, 80.26, H, 5.30.

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