Multi-step Synthesis of Benzopyranones *via* a Key Step Involving Reaction of the Intermediate Compound with Phenyltrimethylammonium Tribromide

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Base catalysed condensation of a substituted 2-hydroxyacetophenone with acetic anhydride and sodium acetate followed by cyclization of the intermediate with acid gave substituted 3-acetyl-2-methyl-4*H*-1-benzopyran-4-ones. These were then brominated with phenyltrimethylammonium tribromide (PTT) to yield the desired 3-(2-bromoacetyl)benzopyran-4-ones. The latter compound on treatment with primary and secondary aryl or alkyl amines, gave the corresponding benzopyran-4-one derivatives.

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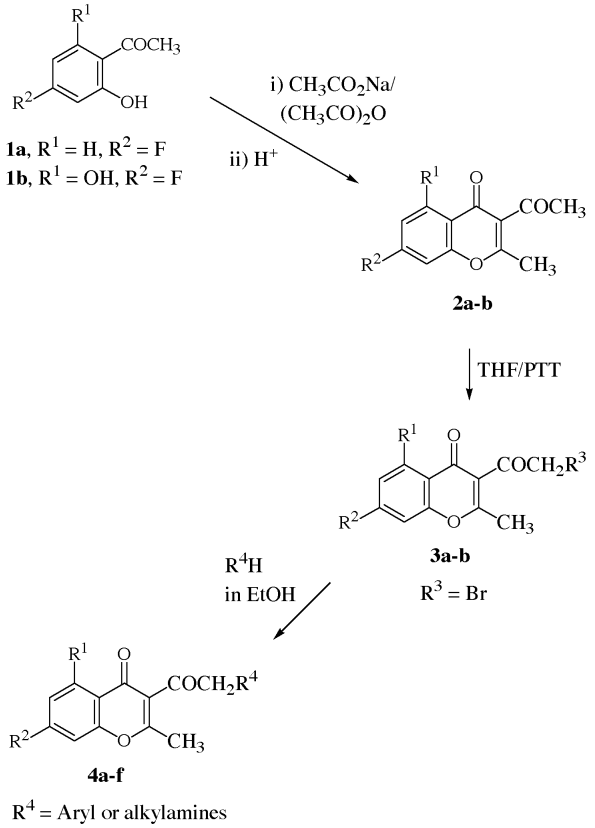
The benzopyran-4-ones incorporating the chromones, chromanones and their naturally occurring analogues flavones are ubiquitous in nature and have been found to play an important role in a number of biological processes [1,2]. In humans, naturally occurring chromones and flavones have shown biological effects [3,4,5]. Flavonoids and isoflavonoids have been described as a gold mine for metabolic engineering [6]. There has been recent interest of flavones as health promoting components of the human diet [7], for example, genistein and daidzein have been reported to be active against a variety of diseases [8,9].

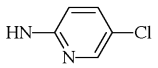
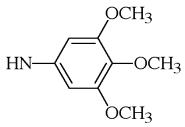
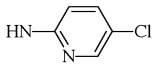
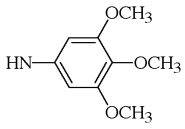
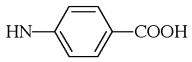
The major precursors of chromones are 2-hydroxyacetophenones and phenols. A wide variety of chromones [2] have been prepared by the claisen condensation reaction of a 2-hydroxyacetophenone and an ester to give the 1,3-diketone, which on subsequent cyclization with acid affords the desired chromone. An alternative source of 1,3-diketone is readily available *via* the *o*-acylation of a 2-hydroxyacetophenone.

Our investigation into a new series of analogues is based on the synthesis, chemistry and pharmacological activity of a variety of benzopyran-4-one derivatives, which have been known to have a wide variety of pharmacological activities [9,10]. This prompted us to modify this ring and explore new activities associated with this nucleus. Thus, we have developed a route that can be utilized to prepare the benzopyran ring system commencing from 2-hydroxyacetophenones (**1a-b**, Scheme 1) containing either the fluoro or a hydroxy functional group that *via* the Baker-Venkataraman rearrangement [5,11] afforded the desired chromones (**2a-b**) possessing the acetyl group at position 3 of the pyran ring.

These types of systems have been reported to undergo bromination with bromine in chloroform at the α-position of the carbonyl group in yields of 65-75% [12,13]. However, in our hands, despite repeated attempts, yields were low (30-42%) after purification. We thus turned our attention towards the use of a more selective and quantitative method of bromination and found that phenyltrimethylammonium tribromide had been previously effective in other unrelated bromination reactions [14,15]. We became interested in this reagent and extended its use for the type of reactions reported herein. Surprisingly, to the best of our knowledge, this reagent has not been reported in the literature for the bromination of 3-acetylbenzopyran-4-ones and interestingly led to improved yields (72-83%) of the 3-(2-bromoacetyl)-benzopyran-4-ones (**3a-b**). The brominated chromones were then treated with a range of primary and secondary alkyl or aryl amines in ethanol to furnish the desired novel

Scheme 1



Entry	Compound	R^1	R^2	R^3	R^4	Yield (%)	m.p [°C]
	2a	H	F	-	-	63	155
	2b	OH	H	-	-	70	117
	3a	H	F	Br	-	72	132
	3b	OH	H	Br	-	83	257
	4a	H	F	-		76	221
	4b	H	F	-		79	210
	4c	OH	H	-		74	216
	4d	OH	H	-		70	181
	4e	OH	H	-		84	179
	4f	OH	H	-		81	165

benzopyran-4-ones (**4a-f**) in high yields (70-84%). Results on the biological effects on blood pressure and cardiac rhythm disturbances, in experimental animals, is currently under study in our pharmacology laboratory.

In conclusion, our synthesis of a series of benzopyran-4-one heterocycles [16-20] has been accomplished in three steps from relatively simple, inexpensive and commercially available starting materials in an efficient manner. The synthesis compares very favorably with other methods [21] reported for similar ring systems and has demonstrated further the utility of phenyltrimethylammonium tribromide in target synthesis. However, in addition, we have successively adopted this robust procedure for the synthesis of a variety of other heterocycles containing different heteroatoms, which will be reported in due course. The flexibility of the approach described herein is thus noteworthy.

EXPERIMENTAL

^{1}H-NMR spectra were recorded on a Bruker 250 MHz instrument in an appropriate deuterated solvent ($CDCl_3$, DMSO, Acetone) with tetramethylsilane as the internal standard. Mass spectra were recorded on a Varian Saturn 3 GC/MS spectrometer.

Infra red spectra were recorded on a Nicolet 205 FT-IR spectrometer. Thin layer chromatography (TLC) was carried out on F_{254} silica gel plates. Solvent system used was 9:1 Toluene: Ethanol. Microanalysis were preformed on an elemental analyzer Perkin-Elmer 2400 CHN.

General Procedure for the Preparation of 3-Acetyl-5-hydroxy (or 7-fluoro)-2-methyl-4*H*-1-benzopyran-4-ones (**2a-b**).

An appropriately substituted 2,6-dihydroxyacetophenone (**1a-b**) (5 g, 37 mmol) and sodium acetate (5 g, 60.1 mmol) was refluxed in 30 ml acetic anhydride. The reaction was monitored by thin layer chromatography with toluene:EtOH (9:1, v/v) and was thus observed to undergo completion within 8 hours. The resulting mixture was then poured into ice:water (50:50, v/v) and the aqueous layer was then removed and the solid or oil so obtained was then washed with water (50 ml). Cyclisation of this intermediate was achieved by boiling with 60 ml of cHCl:EtOH (2:1, v/v). On cooling, the solid so obtained was washed with water and recrystallized from ethanol to give the title compound, 4.98 g (70%) as dark yellow crystals.

General Procedure for the Preparation of 3-(2-Bromoacetyl)-5-hydroxy (or 7-fluoro)-2-methyl-4*H*-1-benzopyran-4-ones (**3a-b**).

To a solution of 3-acetyl-5-hydroxy-2-methyl-4*H*-1-benzopyran-4-one (**2a-b**) (4.98 g, 22.3 mmol) in anhydrous tetrahydrofuran (25 ml) was added phenyltrimethylammonium tribromide (8.62 g, 22.3 mmol) in portions over a period of 10 minutes. The reaction mixture was stirred at room temperature for 6 hours and poured into water (60 ml). THF was removed under reduced pressure and the brown solid so obtained was filtered and recrystallized from ethanol to give the title compound 5.2 g (83%) as light brown crystals.

General Procedure for the Preparation of 2-Methyl-4*H*-1-benzopyran-4-one Derivatives (**4a-f**).

The appropriately substituted 3-(2-bromoacetyl)-2-methyl-4*H*-1-benzopyran-4-one (**3a-b**) (1.0 g, 3.36 mmol) was added to the substituted amine (0.48 g, 5.2 mmol) in ethanol (20 ml). The reaction mixture was refluxed for 2 hours and then cooled. The solid, which separated, was recrystallized from ethanol solvent to furnish the desired compounds.

3-Acetyl-7-fluoro-2-methyl-4*H*-1-benzopyran-4-one (**2a**).

This compound was obtained by condensation of 4-fluoro-2-hydroxyacetophenone (**1a**) with acetic anhydride to give **2a** as dark brown crystals (ethanol), mp 155°; ir: (potassium bromide): 1690 (C=O of γ-pyrone), 1650 (C=O) cm^{-1}. ^{1}H-nmr ($CDCl_3$): δ 2.5 (s, 3H, CH_3), 2.6 (s, 3H, $COCH_3$), 7.0-7.3 (m, 2H Ar), 8.0-8.2 (m, 1H, Ar); ms: m/z: 221 (M^+).

Anal. Calcd. for $C_{12}H_{10}O_4F$ (220.19): C, 65.45; H, 4.12. Found C, 65.53; H, 4.13.

3-Acetyl-5-hydroxy-2-methyl-4*H*-1-benzopyran-4-one (**2b**).

This compound was obtained by condensation of 2,6-dihydroxyacetophenone (**1b**) with acetic anhydride to give **2b** as dark yellow crystals (ethanol), mp 117°; ir: (potassium bromide): 1694 (C=O of γ-pyrone), 1646 (C=O), 3427 (broad OH) cm^{-1}. ^{1}H-nmr ($CDCl_3$): δ 2.50 (s, 3H, CH_3), 2.60 (s, 3H, $COCH_3$), 6.80 (d, 1H, Ar, J = 8.8 Hz), 6.85 (d, 1H, Ar, J = 8.8 Hz), 7.52 (t, 1H, Ar), 12.50 (s, 1H, OH); ms: m/z: 218 (M^+).

Anal. Calcd. for $C_{12}H_{10}O_4$ (218.21): C, 66.05; H, 4.62. Found C, 66.11; H, 4.63.

3-(2-Bromoacetyl)-7-fluoro-2-methyl-4*H*-1-benzopyran-4-one (**3a**).

This compound was obtained by treatment of **2a** with phenyltrimethylammonium tribromide in THF to give **3a** as light brown crystals (ethanol), mp 132°; ir: (potassium bromide): 1690 (C=O of γ-pyrone), 1648 (C=O), 668 (C-Br), 3462 (OH) cm^{-1}. ^{1}H-nmr ($CDCl_3$/DMSO): δ 2.49 (s, 3H, CH_3), 4.71 ($COCH_2Br$), 7.4 (m, 1H, Ar), 7.5 (m, 1H, Ar), 8.2 (m, 1H, Ar) ; ms: m/z: 299, 301 (M^+).

Anal. Calcd. for $C_{12}H_9O_4BrF$ (301.10): C, 48.03; H, 3.02. Found C, 47.91; H, 3.01.

3-(2-Bromoacetyl)-5-hydroxy-2-methyl-4*H*-1-benzopyran-4-one (**3b**).

This compound was obtained by treatment of **2b** with phenyltrimethylammonium tribromide in THF to give **3b** as light brown crystals (ethanol), mp 257°; ir: (potassium bromide): 1696 (C=O of γ-pyrone), 1647 (C=O), 668, 705 (C-Br), 3462 (OH) cm^{-1}. ^{1}H-nmr ($CDCl_3$/acetone-d_6/DMSO): δ 2.57 (s, 3H, CH_3), 4.62 ($COCH_2Br$), 6.80, (d, 1H, Ar, J = 8.8 Hz, H-8,), 6.86 (d, 1H, Ar, J = 8.8 Hz, H-6), 7.54 (t, 1H, Ar), 12.17 (s, 1H, OH); ms: m/z: 297, 299 (M^+)

Anal. Calcd. for $C_{12}H_9O_4Br$ (297.10): C, 46.51; H, 3.05. Found C, 46.40; H, 3.04.

3-[2-(5-Chloropyridin-2-ylamino)-acetyl]-7-fluoro-2-methyl-4*H*-1-benzopyran-4-one (**4a**).

This compound was obtained by condensation of **3a** with 2-amino-5-chloropyridine in ethanol to give **4a** as dark orange crystals (ethanol), mp 221°; ir: (potassium bromide): 1652, 1618 (C=O), 3390 (NH), 1252 (C-F) cm^{-1}. ^{1}H-nmr ($CDCl_3$/DMSO): δ 2.57 (s, 3H,CH_3), 3.6 (s, 2H, CH_2), 3.5-3.6 (s, 1H, NH), 7.2-7.5 (m, 2H, Ar, H-3 of pyridine and H-8 of benzo), 7.6 (d, 1H, Ar, H-5 of benzo J = 8.8 Hz), 7.9 (d, 1H, Ar, H-4 of pyridine J = 8.0 Hz), 8.3 (d, 1H, Ar, H-6 of benzo J = 8.8 Hz), 8.55 (s, 1H, Ar, H-6 of pyridine); ms: m/z: 345 (M^+).

Anal. Calcd.$C_{17}H_{12}N_2O_3FCl$ (346.74): C, 58.88; H, 3.49; N, 8.08. Found C, 58.71; H, 3.48; N, 8.05.

7-Fluoro-2-methyl-3-[2-(3,4,5-trimethoxyphenylamino)-acetyl]-4*H*-1-benzopyran-4-one (**4b**).

This compound was obtained by condensation of **3a** with 3,4,5 trimethoxyaniline in ethanol to give **4b** as cream crystals (ethanol), mp 210°; ir: (potassium bromide): 1666, 1610 (C=O), 3426 (NH), 1256 (C-F) cm^{-1}. ^{1}H-nmr ($CDCl_3$): δ 2.63 (s, 3H, CH_3), 3.89 (s, 9H, OCH_3), 3.96 (s, 2H, CH_2), 3.7-3.9 (s, 1H, NH), 6.55 (s, 2H, Ar H-2, H-5 of trimethoxy benzo), 6.9-7.1 (m, 2H, Ar, H-5,8 of benzo), 8.24 (m, 1H, Ar, H-6 of benzo); ms: m/z: 400 (M^+).

Anal. Calcd.$C_{21}H_{20}NO_6F$ (401.36): C, 62.84; H, 5.02; N, 3.49. Found C, 62.90; H, 5.03; N, 3.50.

3-[2-(5-Chloropyridin-2-ylamino)-acetyl]-5-hydroxy-2-methyl-4*H*-1-benzopyran-4-one (**4c**).

This compound was obtained by condensation of **3b** with 2-amino-5-chloropyridine in ethanol to give **4c** as dark orange crystals (ethanol), mp 216°; ir: (potassium bromide): 1648, 1607

(C=O), 3440 (OH) 3200 (NH) cm^{-1}. ^{1}H-nmr ($CDCl_3$/acetone d_6/DMSO): δ 2.58 (s, 3H, CH_3), 3.6 (s, 2H, CH_2), 3.5 (s, 1H, NH), 6.77 (d, 1H, Ar, J = 8.0 Hz, H-4 of pyridine) 6.97 (d, 1H, Ar, J = 8.0 Hz, H-5 of pyridine), 7.58- 7.68 (m, 2H, Ar, H-2, H-3 of benzo), 8.34 (s 1H, Ar, H-6 of pyridine), 8.61 (d, 1H, Ar, J = 8.8 Hz, H-1 of benzo), 12.65 (s, 1H, OH); ms: m/z: 344 (M^+).

Anal. Calcd $C_{17}H_{13}N_2O_4Cl$ (344.74): C, 59.22; H, 3.80; N, 8.12. Found C, 59.27; H, 3.81; N, 8.14.

5-Hydroxy-2-methyl-3-[2-(3,4,5-trimethoxyphenylamino)-acetyl]-4*H*-1-benzopyran-4-one (**4d**).

This compound was obtained by condensation of **3b** with 3,4,5 trimethoxyaniline in ethanol to give **4d** as cream crystals (ethanol), mp 181°; ir: (potassium bromide): 1666, 1610 (C=O), 3440 (OH), 3390 (NH), 2850 (O-CH_3) cm^{-1}. ^{1}H-nmr (DMSO): δ 2.64 (s, 3H, CH_3), 3.89 (s, 9H, OCH_3), 3.95 (s, 2H, CH_2), 3.8-3.9 (s, 1H, NH), 6.55 (s ,2H, Ar, H-2, H-5 of trimethoxy benzo), 6.71 (d, 1H, Ar, J = 8.8 Hz, H-8 of benzo), 6.76 (d, 1H, Ar, J = 8.8 Hz, H-6 of benzo), 7.48-7.5 (t, 1H, Ar, H-7 of benzo), 13.1 (s, 1H, OH) ; ms: m/z: 398 (M^+)

Anal. Calcd $C_{21}H_{21}NO_4$ (399.40): C, 63.15; H, 5.30; N, 3.50. Found C, 63.27; H, 5.30; N, 3.50.

4-[2-(5-Hydroxy-2-methyl-4-oxo-4*H*-chromen-3-yl)-2-oxoethyl-amino]benzoic Acid (**4e**).

This compound was obtained by condensation of **3b** with 4-aminobenzoic acid in ethanol to give **4e** as light grey crystals (ethanol), mp 179°; ir: (potassium bromide): 1670, 1610 (C=O), 3440 (broad OH), 3300 (NH) cm^{-1}. ^{1}H-nmr ($CDCl_3$/DMSO): δ 2.64 (s, 3H, CH_3), 3.48 (s, 2H, CH_2), 3.4-3.5 (s, 1H, NH), 6.67 (d, 2H, Ar, J = 7.9, Hz H-3, H-5 of benzoic), 6.83 (d, 1H, Ar, H-2, H-6 of benzo J = 8.8 Hz), 7.52 (d, 1H, Ar, J = 8.8 Hz, H-8 of benzo), 7.56 (d, 1H, Ar, J = 8.8 Hz, H-6 of benzo), 8.12 (t, 1H, Ar, H-7 of benzo), 13.1 (s, 1H, OH) ; ms: m/z: 352 (M^+).

Anal. Calcd $C_{19}H_{15}NO_6$ (353.30): C, 65.59; H, 4.28; N, 3.96. Found C, 65.51; H, 4.27; N, 3.95.

5-Hydroxy-2-methyl-3-(2-morpholin-4-yl-acetyl)-4*H*-1-benzopyran-4-one (**4f**).

This compound was obtained by condensation of **3b** with morpholine in ethanol to give **4f** as dark yellow crystals (ethanol), mp 165°; ir: (potassium bromide): 1647, 1608 (C=O), 3448 (broad OH), 3446 (NH); ms: m/z: ($CDCl_3$): δ 2.63 (s, 3H, CH_3), 2.61- 2.76 (m, 8H, Ar of morpholino) 3.73 (s, 2H, CH_2), 3.6-3.7 (s, 1H, NH), 6.64 (d, 1H, Ar, J = 8.8 Hz, H-8 of benzo), 6.67 (d, 1H, Ar, J = 8.8 Hz, H-6 of benzo), 7.54-7.57 (t, 1H, Ar, H-7 of benzo), 12.43 (s, 1H, OH); ms: m/z: 314 (M^+).

Anal. Calcd $C_{17}H_{17}NO_5$ (315.32): C, 64.74; H, 5.43; N, 4.44. Found C, 64.89; H, 5.44; N, 4.45.

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