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The Synthesis of Benzopyran Analogues with Variation at C-2, C-4 and C-7 Positions

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ABSTRACT

Benzopyran derivatives were efficiently synthesized by the reaction of acetophenone and acetic anhydride in the presence of base for excellent yield. The methodology comprise of four main steps Friedel-Crafts acylation proceeded by aldol condensation, methoxylation, reduction and esterification. Substituted phenol was first acylated with acetic acid in presence of Lewis acid to substituted acetophenone which was smoothly converted to benzopyran, by condensing with substituted ketones in presence of a base such as Amberlite through the aldol condensation reaction. $^1\text{H-NMR}$, IR, MASS spectra analysis conclusively confirmed the structure of 2,2-Dimethyl-7-hydroxy-3,4-dihydro-2H-1-benzopyran-4-one, 2,2-Dimethyl-3,4-dihydro-7-methoxy-2H-1-benzopyran-4-one, 2,2-dimethyl-7-methoxy-6-nitro-3,4-dihydro-2H-1-benzopyran-4-one.

Key words: Benzopyran-4-one, Amberlite, ethyl acetate, NMR, IR, acetophenone

INTRODUCTION

Benzopyran and their derivatives have shown various pharmacological and biological properties (Negi *et al.*, 2011). The initial euphoria over the discovery of benzopyran based potassium channel opening as a mechanism for the vasodilator/antihypertensive activity of several existing agents is slowly settling down (Cassidy *et al.*, 1992). The diversity of benzopyran based potassium channels in various tissues and their roles in controlling basic cell functions are being unravelled by interdisciplinary research. Since there are several types of potassium channels, often in the same tissue, channel and tissue selectivity plays a major role in advancing these agents up to clinical stage. Benzopyran is used in the treatment of hypertension (Singh *et al.*, 2011). Although, most of the pharmacological effects of the benzopyran based K_{ATP} openers (e.g., cromakalim) are reversed by sulfonyl urea type K_{ATP} blockers (e.g., glyburide), cromakalim and other K_{ATP} openers do not effect glyburide binding at therapeutically relevant concentration definitive experiments need to be performed to understand at what level the effects of potassium channel openers are reversed by sulfonyl ureas. Additional complication comes from the controversy over the identity of the potassium channel(s) affected by cromakalim and other prototype compounds (Riepe *et al.*, 1992).

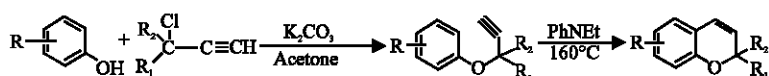
The availability of organic molecules in large numbers that modulate these channels in a tissue-specific manner would be useful to explore the therapeutic potential of potassium channel modulation. Medicinal chemistry research has so far concentrated only on modification of the existing molecules. The design of molecules which are channel and tissue-specific relies heavily on the progress in understanding the structural biology and the protein chemistry of benzopyran based potassium channels (Bergmann and Gericke, 1990). At the present time, little is known about

the three dimensional structure of channel protein(s) or the second messenger systems that regulate their activity (Gericke *et al.*, 1991). Our understanding of the basic mechanism(s) of channel functioning is slowly progressing but further work is needed to unravel how various channels differ in structure and in their gating properties. This is very crucial for understanding pharmacological profile of existing potassium channel modulators (Thompson *et al.*, 2003). There has been a rapid extension in the syntheses of molecules related to nicorandil, cromakalim, pinacidil in last few years (Tripathi *et al.*, 2009).

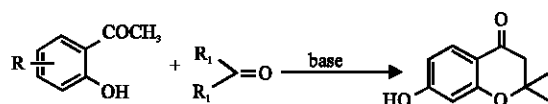
It have taken attention of the researchers, chemists and pharmacologists to synthesised new drugs which are more potent, less toxic and at the same time better tolerated than existing drugs (Nikalje *et al.*, 2011). Reports of work on the pyridine regiomers or substitution of other amides for the pyrrolidinone have appeared already in the literature. Cromakalim by far remains the most mimicked structure in this class of compounds. The 6-Substituted-2,2-bis (fluoromethyl) benzopyran-4-carboxamide potassium channel openers showed a highly potent, slow and long-lasting antihypertensive effect with reduced reflux tachycardia, together with the beneficial effects of potassium channel openers such as improvement in lipid metabolism (Burrell *et al.*, 1990).

In the literature there are several synthetic routes described for the construction of benzopyran nucleus. The most common and facile method used for the preparation of 2,2-dimethyl-2H-benzopyran-4-one is the reaction between a phenol such as resorcinol and α , β -unsaturated carboxylic acid such as β - β -dimethyl acrylic acid in presence of a strong acid catalyst. The pyranones can easily be converted to corresponding chromenes via reduction and dehydration (Horino *et al.*, 1998).

The pyrone ring is also easily obtained from corresponding coumarin through well known Grignard reaction Propargyl ethers of phenols are also reported to produce chromenes via Claisen rearrangement in good yields. The Claisen rearrangement can be effected in presence of diethylamine in benzene at elevated temperature (Cho *et al.*, 1996).



Another common route for building of benzopyran system is through the reaction of ortho hydroxy acetophenone with appropriate alkyl ketones or aldehydes in presence of a base.



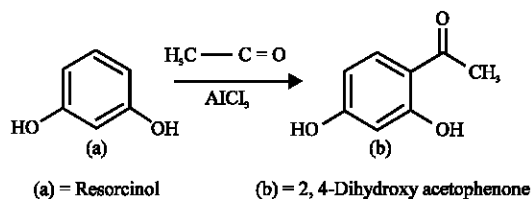
In the above equation substituted chromanones with variation at C-2 positions can easily be obtained in high yields.

MATERIALS AND METHODS

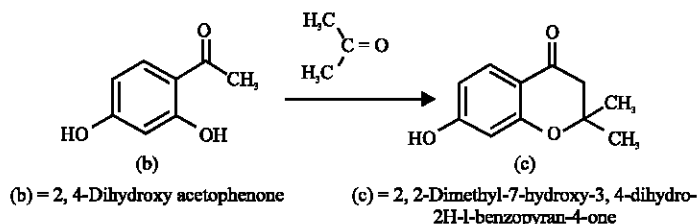
Chemicals and reagents: Solvents, chemicals and reagents were used of are analytical grade (Yao *et al.*, 2007) 0% aqueous sulphuric acid containing 7.0 g Ceric ammonium sulphate (per 100 mL of the solution), 2,4-dinitrophenyl hydrazine (5% ethanol solution) were used as spray reagents, resorcinol, acetic anhydride, aluminium chloride, amberlite. UV or iodine vapours, alumina coated aluminium TLC sheets, UV fluorescent silica gel, column chromatography.

Method: The derivatives of benzopyran was synthesized by friedel-Crafts acylation, aldol condensation, methoxylation and reduction.

Preparation of 2,4-Dihydroxy acetophenone by friedel-crafts acylation: Anhydrous aluminium chloride (16.5 g, 0.12 mol) was dissolved in 15.8 mL (0.27 mol) of acetic anhydride, in a 250 mL round bottomed flask with a guard tube heated mixture and add resorcinol (11 g, 0.1 mole) with constant stirring. The solution was heated on oil bath until it begins to just boil and the temperature was maintained at 159°C. The heating was stopped and the reaction allowed to complete. After standing for half an hour, the solution was diluted with a mixture of 50% hydrochloric acid. The dark red solution was placed in an ice bath. The resulting precipitate were collected on a filtration funnel and washed with 750 mL of dilute (30%) hydrochloric acid. This orange red product was chromatographed over silica gel (60-120 mesh) and eluted with petroleum ether and ethyl acetate to give pure product followed by ¹H-NMR, IR (Ho *et al.*, 2008).

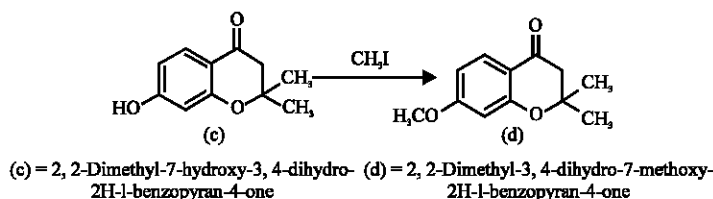


Preparation of 2,2-Dimethyl-7-hydroxy-3,4-dihydro-2H-1-benzopyran-4-one by aldol condensation: Amberlite (3.55 gm, 0.05 mole) was added to the solution of 2,4-dihydroxy acetophenone (7.6 gm, 0.05 mole) and acetone (2.7 gm, 0.05 mole) in dry toluene (40 mL). Then the mixture was refluxed on water bath for 6 h. After cooling down to room temperature, the mixture was poured into ice water and acidified with 5% hydrochloric acid. The product was extracted with ethyl acetate and was dried over sod. sulphate (Na₂SO₄) distilled under vacuum to give a dark residue (Joshi and Gopal, 2011). The product was chromatographed over silica gel (petroleum ether: ethyl acetate, 80:20) as eluent to give pure product though aldol condensation followed by ¹H-NMR, IR, Mass spectra (Zhu *et al.*, 2006).

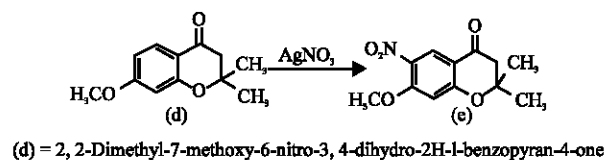


Preparation of 2,2-Dimethyl-3,4-dihydro-7-methoxy-2H-1-benzopyran-4-one by 2,2-Dimethyl-7-hydroxy-3,4-dihydro-2H-1-benzopyran-4-one by methoxylation: To a solution of 2,2-Dimethyl-7-hydroxy-3,4-dihydro-2H-1-benzopyran-4-one (1.92 g, 0.1 mole) acetone (20 mL), anhydrous pot carbonate (2.50 g.) methyl iodide (1.42 g, 0.01 mole) were added. The reaction mixture was refluxed on water bath the monitoring of the reaction was done by TLC. The reaction was complete after 3 h. The contents were cooled filtered through sintered funnel finally

concentrated by distillation under vacuum. The product obtained was chromatographed over silica gel column using petroleum ether-ethyl acetate (96:4) as eluant to give the pure product followed by ¹H-NMR, IR, Mass spectra.



Preparation of 2,2-dimethyl-7-methoxy-6-nitro-3,4-dihydro-2H-1-benzopyran-4-one by reduction: A stirred cold (5°C) slurry of 2,2-dimethyl-7-methoxy-3,4-dihydro-2H-1-benzopyran-4-one (1.82 g, 0.01 mole) AgNO₃ (1.69 g, 10 mmol) in chloroform (10 mL) was treated dropwise with trifluoroacetic anhydride (5 mL). The initial colorless reaction mixture soon attained the brown colour. It was stirred at 5°C for 6 h at room temperature for 12 h. After the completion of the reaction, the organic layer was washed with water dried with Na₂SO₄ and the organic layer was concentrated by distillation under vacuum. The product obtained was chromatographed over silica gel using petroleum ether: ethyl acetate (85:15) to give pure product followed by ¹H-NMR, IR, Mass spectral data.



RESULTS

Spectral studies

2, 4-Dihydroxy acetophenone:

- **IR:** 3240, 2845, 1646, 1605, 1522, 1451, 1430, 1394, 1340, 1290, 1220, 1140, 1080, 991, 960, 840, 790, 733, 705, 660, 600 cm⁻¹
- **¹H NMR (CDCl₃) δ:** 2.55 (3H, s, CH₃), 6.40 (1H, d, J = 2.5 Hz, 3-H), 6.38 (1H, dd, J = 8.52 and 2.4 Hz, 5-H), 7.60 (1H, d, J = 8.5 Hz, 6-H)

2, 2-Dimethyl-7-hydroxy-3, 4-dihydro-2H-1-benzopyran-4-one:

- **IR:** 3128, 1635, 1605, 1585, 1494, 1400, 1382, 1362, 1349, 1271, 1172, 1130, 1084, 1057, 1020, 992, 860, 823, 787, 761 cm⁻¹
- **¹H NMR (CDCl₃) δ:** 1.55 (6H, s, 2xCH₃), 2.87(2H, s, CH₂), 6.38(1H, d, J = 2.4 Hz, 8-H), 6.58 (1H, dd, J = 8.3 Hz and 2.7 Hz, 6-H), 7.89 (1H, d, J = 8.5 Hz, 5-H)
- **MS at m z⁻¹:** M⁺ at m/e 193(11), 191(64), 177(91), 151(10), 135(103), 137(59), 104(53), 80(22), 68(16), 66(15)

2, 2-Dimethyl-3, 4-dihydro-7-methoxy-2H-1-benzopyran-4-one:

- **IR:** 2990, 1671, 1619, 1612, 1593, 1441, 1380, 1365, 1322, 1270, 1110, 1061, 1023, 960, 981, 844, 822, 760 cm^{-1}
- **$^1\text{H-NMR}(\text{CDCl}_3)$:** 1.49 (6H, s, 2-H), 2.65 (2H, s, 3-H), 3.87 (3H, s, 7-H), 6.41(1H, d, J = 2.5 Hz, 8-H), 6.63 (1H, dd, J = 8.5 and 2.5 Hz, 6-H), 7.81 (1H, d, J = 8.5 Hz, 5-H)
- **MS at m z⁻¹:** M⁺ at m/e 205 (86), 191 (20), 193 (82), 154 (100), 157 (66), 125 (57), 105 (66), 97 (21), 89 (25), 85 (23), 79 (51), 69 (24), 63 (41)

2, 2-dimethyl-7-methoxy-6-nitro-3, 4-dihydro-2H-1-benzopyran-4-one:

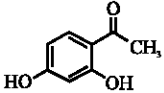
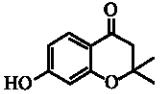
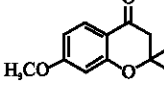
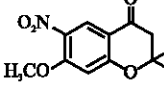
- **IR:** 2910, 1671, 1619, 1612, 1597, 1443, 1381, 1359, 1327, 1273, 1121, 1065, 1020, 960, 970, 840, 810, 765 cm^{-1}
- **$^1\text{H-NMR}(\text{CDCl}_3)$:** 1.49 (6H, s, 2-H), 2.67 (2H, s, 3-H), 3.85 (3H, s, 7-H), 6.47 (1H, d, J = 2.5 Hz, 8-H), 6.58 (1H, dd, J = 8.5 and 2.5 Hz, 6-H), 7.87 (1H, d, J = 8.5 Hz, 5-H)
- **MS at m z⁻¹:** M⁺ at m/e 205 (85), 195 (19), 190 (81), 151 (100), 150 (67), 132 (55), 105 (65), 94 (23), 90 (25), 81 (24), 79 (53), 67 (21), 63 (43)

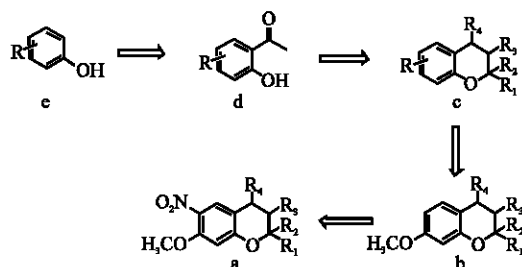
DISCUSSION

Retro synthetic pathway for the construction of proposed novel benzopyran-4-one nucleus is delineated in the Table 1.

Retro synthesis: On the basis of ease of availability of starting materials/chemicals, variability of substitution higher yields were investigated to utilize the method described above using o-hydroxy acetophenone for the synthesis of substituted benzopyran analogues. The retro-synthetic route to proposed methodology uses direct condensation reaction between a substituted phenol (o-hydroxy acetophenones) a keto (acetic anhydride) compound in presence of a base (Azad *et al.*, 2007).

Table 1: Structure, molecular formulae and yield of benzopyran-4-one derivatives

Structure	Molecular For.	Yield (%)
	$\text{C}_8\text{H}_8\text{O}_3$	88
	$\text{C}_{11}\text{H}_{12}\text{O}_3$	92
	$\text{C}_{12}\text{H}_{14}\text{O}_3$	98
	$\text{C}_{12}\text{H}_{13}\text{NO}_5$	90

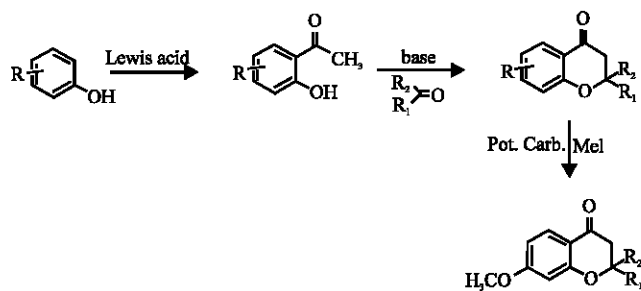


The proposed synthetic methodology comprises four main steps friedel craft acylation proceeded by aldol condensation, than methoxylation, reduction, esterification friedel-craft's acylation.

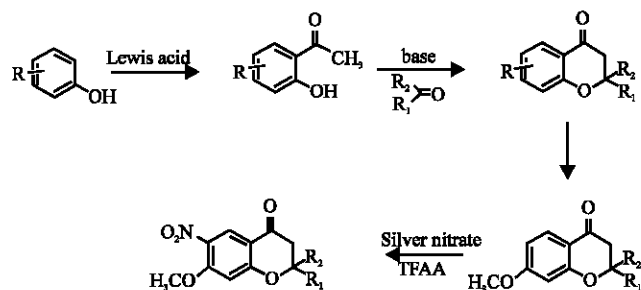
Compounds have been synthesized and their structures have been confirmed from their spectral data (Mandge *et al.*, 2007).

Substituted phenol was first acylated with acetic acid in presence of lewis acid to substituted acetophenone (friedel craft acylation) which was smoothly converted to benzopyran, by condensing with substituted ketones in presence of a base such as amberlite (aldol condensation). The phenolic group was methylated in 98% yield the methylated product was nitrated finally.

Graphical Abstract-1:



Graphical Abstract-2:



CONCLUSION

It has been concluded that, synthesis of benzopyran-4-one derivatives using friedel craft acylation proceeded by aldol condensation, than methoxylation in the presence amberlite as base in good to excellent yield. The simplicity of reaction high, short time of reaction offer improvements over many existing method.

ACKNOWLEDGMENT

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