A 'One Pot' Synthesis of 2-Aryl-4*H*-1-benzopyran-4-ones Under Coupled Microwave Phase Transfer Catalysis (PTC) and Ultrasonic Irradiation PTC

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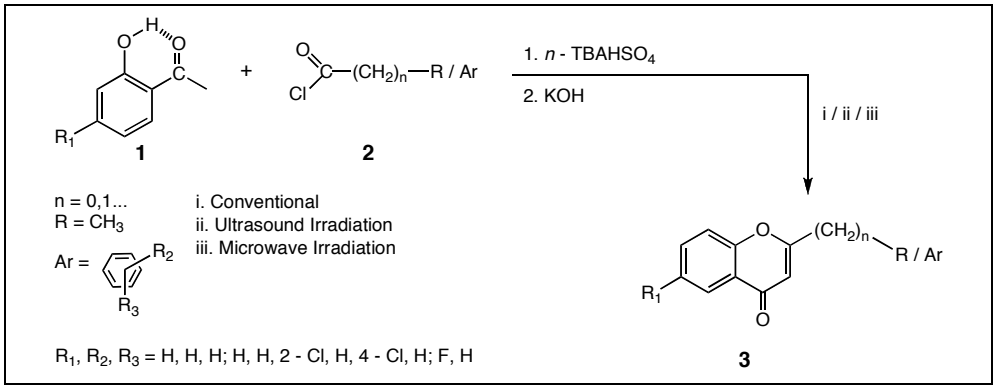

A 'one pot' synthesis of 2-aryl-4*H*-1-benzopyran-4-ones **(3a-3f)** is being reported. A mixture of *o*-hydroxyacetophenone, aroyl chloride, powdered *n*-tetrabutylammonium hydrogensulphate (*n*-$TBAHSO_4$) and potassium hydroxide (KOH) were either irradiated by microwaves or sonicated in an ultrasonic cleaning bath to afford flavones directly. On the contrary, conventional liquid-liquid Phase Transfer Catalysis (PTC) using benzene as organic phase and aqueous KOH as the second phase afforded first β-diketones in accordance with Baker-Venkataraman synthesis which upon cyclization by *p*-toluenesulphonic acid (*p*-TSA) gave desired flavones in the next step. PTC coupled with microwaves or ultrasound show enhanced yields, the clean reaction conditions require less time, and have easier workup protocol. All synthesized compounds were characterized by their Proton Magnetic Resonance (PMR), IR, FAB Mass and elemental analyses.

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INTRODUCTION

Flavones are a class of naturally occurring compounds present in a wide variety of plants, seeds, citrus fruits, olive oil, tea and red wine and are commonly consumed with human diet [1-2]. Most of the current synthesis for new flavanoids are based on the pioneer work developed by Robinson [3] and Venkataraman [4] and despite the number of steps involved in the both these methods, they still constitute the most popular methodologies currently used for preparation of flavanoids. These synthetic effects are due both to their chemotaxonomical interest as biological markers [5] and to the increasing importance of their multiple biological activities: leishmanicidal activity [6], ovipositor stimulant phytoalexins [7], anti-HIV [8], vasodilator [9], anti-viral [10], anti-oxidants [11], bactericidal [12], DNA cleavage [13], anti-inflammatory [14], anti-mutagenic [15], anti-allergic [16] and anti-cancer [17].

The incorporation of electronegative elements, such as halogens, in the flavonoid structure, introduces new patterns of biological properties. 4',6-Dichloroflavon has been reported to be a potent antirhinovirus compound [18]. Halogenated flavones exhibit structure-dependent aryl hydrocarbon receptor (AhR) agonist and antagonist activities comparable to that observed for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin TCDD [19]. One of the most recent study reports the effect of some flavonoids on the central nervous system [20]. Halogenated flavanones are considered potential benzodiazepine receptor ligands [21].

The general method to obtain flavones are the cyclization of 1,3-diphenylpropane-1,3-diones or 2'-hydroxychalcones, which are prepared from 2'-hydroxyacetophenones and benzoylating reagents or benzaldehydes [22]. In the Baker-Venkataraman process [23,24], 2'-hydroxyacetophenones are converted into benzoyl esters, which are rearranged with bases to form 1,3-diphenylpropane-1,3-diones, followed by cyclization with sodium acetate [23a] or sulphuric acid [23b,c] in acetic acid, I_2-DMSO [25], and Co^{III}(salpr)(OH) [(Salpr) = N^1,N^7–4–azaheptamethylenebis-(salicylideneiminato)] [26] to yield flavones in three steps. Although the reaction of 2'-hydroxyacetophenones and benzoyl chlorides [27] or methyl benzoates [28] with bases affords 1,3-diphenylpropane-1,3-diones directly, these methods required excess benzoylating reagents or bases.

The oxidative cyclodehydration of 2-hydroxychalcones with $NiCl_2$/Zn/KI [29], $NaIO_4$-DMSO [30] and iodosobenzene diacetate [31] also leads to the formation of flavones, but this process requires high reaction temperature. Other methods to synthesize flavones include the coupling of 2-iodophenols with phenylacetylenes in the presence of secondary amine and $PdCl_2$ (dppf) [32], but only a few examples of flavones from these techniques have been reported.

All the above discussed methods are cumbersome requiring two or three steps and involve lengthy work-up procedures. So, now we wish to report a simple 'One Pot' strategy for synthesizing 2-aryl-4*H*-1-benzopyran-4-ones **(3a-3f)** (Scheme 1) coupling PTC with either microwave or ultrasound irradiation.

Phase Transfer Catalysis (PTC) allows one to perform many reactions that otherwise proceed unsatisfactorily or do not proceed at all due to the reactants being present in different phases. It minimizes the two important deactivating forces *viz*. solvation and ion pairing. PTC is now well established as a 'Green Chemistry Technique'. PTC coupled with non-conventional energy sources like microwaves and ultrasonic irradiations offers the advantage of accomplishing reaction at ambient pressure, thus providing unique chemical process with special attributes such as enhanced reaction rates, higher yields and the associated ease of manipulation. Heterogenous reactions facilitated by supported reagents on inorganic oxide surfaces have received attention in recent years [33].

In light of above observations and in continuation to our previous work on bioactive fluorinated/non-fluorinated heterocycles and PTC, we thought it worthwhile to synthesize derivatives of these biologically useful heterocycles by using a simple, convenient and mild phase transfer catalyzed heterocyclization approach leading to the synthesis of desired product *via* PTC induced by microwaves or ultrasound irradiation. Since the compounds may be potentially bioactive they would be sent for screening for their anti-inflammatory and anti-tumor activities.

PTC, microwave and ultrasound (non-conventional methods) all are now recognized as environmentally benign alternatives to conventional methods.

In conclusion, we report three comparative strategies for the preparation of 2-aryl-4*H*-1-benzopyran-4-ones. It is observed that out of the three methods, microwave irradiated reactions occur in faster (<10 minutes), give higher yield (>80%), have simpler reaction procedures and eliminate the use of solvents. When the reaction mixture was irradiated in domestic microwave for a longer time (greater than 10 minutes) and in excess amount of aroyl chloride (> 12 mmol), the aroylation also occurred at position – 3 in the presence of PT catalyst.

RESULTS AND DISCUSSION

2-Aryl-4*H*-1-benzopyran-4-ones **(3a-3f)** were synthesized by employing various reaction conditions *viz*., classical, ultrasonic radiations and microwave PTC approach. In the classical approach *o*-hydroxyacetophenone/5-fluoro-2-hydroxyacetophenone **(1)** was treated with substituted aroyl chlorides **(2)** under PTC conditions to give β-diketones which in turn on cyclization with *p*-toluenesulphonic acid (*p* – TSA) afforded the substituted 2-aryl-4*H*-1-benzopyran-4-ones **(3)** in good yield.

Scheme 1

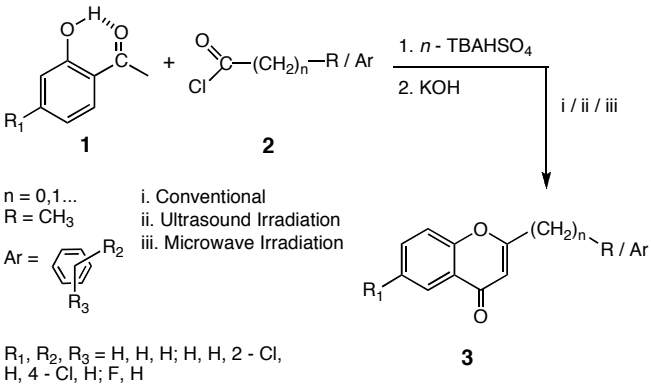

Table 1: Physical and Analytical Data of compounds **(3a-f)**

Compd. No.	R	R_1	R_2	R_3	n	Mol. For.	m.p.[Ref] °C	Analysis % Calcd./Found C	H	Yield % i	ii	iii
3a	-	H	H	H	0	$C_{15}H_{10}O_2$	95-96[24]	81.08 81.12	4.50 4.51	70	75	81
3b	-	H	H	2 -Cl	0	$C_{15}H_9O_2Cl$	185-187	70.17 70.26	3.51 3.50	72	76	83
3c	-	H	4 -Cl	H	0	$C_{15}H_9O_2Cl$	251-253[34]	70.17 70.26	3.51 3.52	71	74	85
3d	-	F	H	H	0	$C_{15}H_9O_2F$	99-103	75.00 75.25	3.75 3.74	74	77	84
3e	-	H	H	H	1	$C_{16}H_{12}O_2$	146-149	81.36 81.47	5.08 5.07	75	79	85
3f	CH_3	H	H	H	8	$C_{19}H_{26}O_2$	Viscous	79.72 79.64	9.09 9.10	69	71	79

i) Conventional, ii) Ultrasonic Irradiation, iii) Microwave Irradiation, *Reference Number

In the ultrasonic approach *o*-hydroxyacetophenone/5-fluoro-2-hydroxyacetophenone **(1)** and substituted aroyl chlorides **(2)** under PTC conditions were sonicated for 2-3 hours to afford the desired products **(3)** in higher yield and shorter reaction time than the classical approach.

The same reactants without benzene were thoroughly mixed and irradiated for 250-300 seconds in a domestic microwave oven to afford the desired products in higher yield and lesser time in contrast to conventional process. The results are presented in Table 1. All the synthesized compounds were characterized on the basis of their analytical and spectral (IR, ^{1}H NMR and FAB Mass) data which agreed well with assigned structures (Table – 2).

Table 2: Spectroscopic data of 2-aryl-3*H*-1-benzopyran-4-one (**3a-f**)

Compd. No.	IR ν_{max} (cm^{-1}) (KBr)	^{1}H NMR δ (ppm) ($CDCl_3$)	FAB Mass m/z (M^++1)
3a	3071(aromatic C-H str.), 1646 (>C=O), 1606 (aromatic >C=C< str.), 1129 (C-O-C)	(DMSO-d_6): 8.26 (dd, ^1J = 7.9 Hz, ^2J = 1.62 Hz, 1H), 7.94-7.98 (m, 2H), 7.62-7.76 (m, 1H), 7.52-7.59 (m, 4H), 7.43-7.48 (m, 1H), 6.9 (s, 1H)	223
3b	3090 (aromatic C-H str.), 1642 (>C=O), 1606 (aromatic >C=C< str.), 1090 (C-O-C), 828 (C-Cl)	(DMSO-d_6): 8.25 (dd, ^1J = 7.9 Hz, ^2J =1.62 Hz, 1H), 7.74 (d, J = 7.14 Hz, 2H), 7.70-7.75 (m, 1H), 7.58 (d, J = 8.61 Hz, 1H), 7.42-7.47 (m, 1H), 7.52 (d, J = 7.14 Hz, 2H), 6.8 (s, 1H)	257 / 259
3c	3142 (aromatic C-H str.), 1647 (>C=O), 1590 (aromatic >C=C< str.), 1010 (C-O-C), 875 (C-Cl)	(DMSO-d_6): 8.1 (dd, ^1J =7.9 Hz, ^2J = 1.62 Hz, 1H), 7.74 (d, J = 7.74 Hz, 2H), 7.73-7.76 (m, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.40-7.50 (m, 1H), 7.47 (d, J = 7.14 Hz, 2H), 7.01 (s, 1H)	257 / 259
3d	3065 (aromatic C-H str.), 1675 (>C=O), 1600 (aromatic >C=C< str.), 1130 (C-O-C), 1075(C-F)	(DMSO-d_6): 8.1 (d, J = 7.30, 1H), 7.87-7.92 (m, 1H), 7.55 (d, J = 6.06 Hz, 2H), 7.26-7.49(m, 5H), 6.8 (s, 1H)	241
3e	3072 (aromatic C-H str.), 2875 (aliphatic C-H str.), 1608 (C-O-C), 1500 (aromatic >C=C< str.), 1010 (>C=O)	(DMSO-d_6): 7.69 (dd, ^1J = 8.04 Hz, ^2J = 1.44 Hz, 1H), 7.52-7.58 (m, 2H), 7.42-7.46 (m, 1H), 7.30-7.40 (d, J = 8.4 Hz, 1H), 7.40-7.50 (m, 5H), 7.01 (s, 1H), 3.01 (s, 2H), 2.42 (s, 2H)	237
3f	3072 (aromatic C-H str.), 1646 (>C=O), 1606 (aromatic >C=C< str.), 1129 (C-O-C)	(DMSO-d_6): 8.1 (dd, ^1J = 7.98 Hz, ^2J = 1.42 Hz, 1H), 7.51-7.64 (m, 2H), 7.41-7.48 (m, 1H), 6.69 (s, 1H), 1.36-1.44 (m, 2H), 1.73-1.78 (m, 16H)	287

EXPERIMENTAL

All the melting points were determined in open glass capillary tubes and are uncorrected. The IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin Elmer 557 grating infrared spectrophotometer in KBr pellets. PMR spectra were recorded on JEOL AL 300 spectrometer (300 MHz) using $CDCl_3$ as a solvent. TMS was used as internal standard (chemical shift in δ, ppm) at Department of Chemistry, University of Rajasthan, Jaipur. The FAB mass spectra were recorded on a JEOL SX 102/DA-6000 Mass spectrometer / Data system using Argon / Xenon (6KV, 10mA) as the FAB gas at Central Drug Research Institute (CDRI), Lucknow. Reactions were carried out in an LG MS-194 A household microwave oven with maximum 800 power. Sonication was carried out in a Toshion, Model SW 4 cleaner with a frequency of 37 Hz and a power of 150 watts. The purity of the compounds was checked by TLC using silica gel (60 – 120 mesh) as adsorbent, UV light or iodine accomplished visualization. *o*-Hydroxyacetophenone, aroyl chlorides, KOH, *n*-$TBAHSO_4$ are all commercial products and were used without further purification. 5-Fluoro-2-hydroxyacetophenone was prepared by literature method [33].

General Procedures for the preparation of 2-aryl-4*H*-1-benzopyran-4-ones (3a-3f).

Method (i) *o*-hydroxyacetophenone/5-fluoro-2-hydroxy-aceto-phenone **(1)** (3.0 mmol) and substituted aroyl chlorides **(2)** (3.6 mmol) in benzene (20 mL) were magnetically stirred at 80 °C with KOH solution (50%; 20 mL) in the presence of *n*-$TBAHSO_4$ (1.5 mmol, 0.51 g) for 2-3 hours until the starting acetophenone and the first formed *o*-aroyloxyacetophenone disappeared (TLC). During this period the benzene solution acquired a deep yellow to orange color. The benzene layer was separated, washed thoroughly with water (3*100 mL) and from the separated benzene layer the water was removed by azeotropic distillation. To this reaction mixture *p*- toluene-sulphonic acid (9.0 mmol, 1.71 g) in dry benzene (25-50 mL) was added. The reaction mixture was further refluxed and the water generated in the reaction was azeotropically removed (30-45 minutes). Excess *p*-toluenesulphonic acid was extracted from the benzene solution with sodium hydrogen carbonate solution (8%; 50 mL). Benzene was distilled off and the residue dried under *vacuo* over phosphorus pentoxide. The residue was recrystallized from ethyl acetate - light petroleum ether or benzene - light petroleum ether to give the desired product.

Method (ii): A mixture of *n*-$TBAHSO_4$ (10 mmol, 3.39 g) and KOH (20 mmol, 1.12 g) was grinded together in a mortar. Then this mixture was transferred into a pyrex conical flask (100 mL). *o*-Hydroxyacetophenone / 5-fluoro-2-hydroxyacetophen-one **(1)** (10 mmol) and substituted aroyl chloride **(2)** (12 mmol) were added to it and irradiated in an ultrasonic cleaning bath for 120-150 minutes at a temperature of 35-40 °C. The reaction flask was located in the maximum energy area in the cleaner. The bath temperature was controlled by the addition or removal

of water. The progress of reaction was monitored by TLC using C_6H_6:EtOAc:90:10 as solvent system. After cooling to room temperature, HCl (2 *N*; 25 mL) was added, the reaction was extracted with chloroform and the product was purified by column chromatography using silica gel (60 – 120 mesh) as stationary phase and solvents of increasing polarity as mobile phase. Pure flavone was obtained in benzene: pet-ether (4:1) as yellow crystalline needles.

Method (iii): A mixture of *n*-$TBAHSO_4$ (10 mmol, 3.39 g) and KOH (20 mmol, 1.12 g) was grinded together in a mortar. Then this mixture was transferred into a conical flask (100 mL). *o*-hydroxyacetophenone/5-fluoro-2-hydroxyacetophenone **(1)** (10 mmol) and substituted aroyl chloride **(2)** (12 mmol) was added to it and irradiated with microwaves for 5-6 minutes at full power (800 W). Final temperature of the reaction was measured with the help of a thermometer at the end of the reaction. The progress of reaction was monitored by TLC using C_6H_6:EtOAc: 90:10 as solvent system. After cooling to room temperature, HCl (2 *N*; 25 mL) was added, the reaction was extracted with chloroform and the product was purified by column chromatography using silica gel (60 – 120 mesh) as stationary phase and solvents of increasing polarity as mobile phase. Pure pyran – 4 - ones were obtained in benzene: pet-ether (4:1) as yellow crystalline needles.

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