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A Facile Microwave Assisted Synthesis and Antimicrobial Activity of Some Active Intermediates

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ABSTRACT

The concept of green chemistry is now widely adopted to meet the scientific challenges of protecting the human health and environment. Microwave heating is very attractive for chemical applications and has become a widely accepted non-conventional energy source for performing organic synthesis. We schematized here a microwave assisted synthesis of some active intermediates such as substituted chromones (3a-b), substituted acrylophenones (4a-l) of biological importance by using substituted 1,3–propanediones(2a-c) in presence of catalysts PPA and TEBA. Claisen condensation of (1a-c) with ethyl acetate under powerful basic medium afforded corresponding diketones (2a-c). Cyclization of (2a-c) in presence of inorganic polymer (PPA) afforded corresponding chromones (3a-b). Condensation of (2a-c) with substituted aldehydes in presence of phase transfer catalyst (TEBA) afforded the corresponding acrylophenones (4a-l). The structures of the synthesized compounds have been confirmed on the basis of chemical analysis , spectral analysis (IR, ^{1}H-NMR) and elemental analysis. The purity of compounds has been checked by HPLC technique. Some of synthesized compounds have been screened for their antimicrobial activities.

Keywords: Microwave irradiation, 1,3-propanediones, PPA, TEBA, chromones, acrylophenones, antimicrobial activity.

INTRODUCTION

Since last decade there has been a stress to work in the area of ‘green chemistry’. To achieve such goal, elimination of hazardous chemicals which minimizes waste generation and benign sustainable courses are required. Much work in this direction for synthetic methodologies has been

adopted[1] for Chemical processes[2]. Utilization of nontoxic chemicals, environmentally benign solvents, and renewable materials are some of the key issues that merit important consideration in green synthetic strategies[3]. One of the novel approaches towards clean and green chemistry is the application of microwaves, which is relatively a convenient, safe and rapid methodology as reported by our lab[4]. So we schematized here synthesis of various intermediates such as substituted chromones and substituted acrylophenones under thermal and microwave heating which are highly bioactive and are widely used in pharmaceuticals since the late 1980s[5].

Many biologically active compounds found in the literature have chromone and acrylophenone moieties in their structures[6-9]. Chromones constitute one of the major classes of naturally occurring compounds and interest in their chemistry continues unabated because of their usefulness as biologically active agents[10]. Some of biological activities attributed to choromone derivatives include cytotoxic (anticancer)[11], neuroprotective[12], HIV-inhibitary[13], antimicrobial[14], antioxidant activity[15]. Due to their abundance in plants and their low mammalian toxicity, chromone derivatives are present in large amounts in the human diet[16]. Recently acrylophenone derivatives were found to be associated with biological activities such as antibacterial[17], antifungal[18], insecticidal[19], anaesthetic[20], anti-inflammatory[21], analgesic[22], ulcerogenic[23], etc. It is now well established that the phase transfer catalyst (PTC) reactions have considerable advantages over the conventional processes. The PTC reactions do not require vigerous conditions, expensive aprotic solvents, high temperature etc. The PTC reactions are fast, easy to work up and give high yields. Most of the heterocyclic compounds have been synthesized by using PTC[24-27].

Keeping in view the potential biological activities of substituted chromonoes and acrylophenones, it was promoted us to synthesize such an active intermediates by using catalysts like PPA, benzyl triethyl ammonium chloride (TEBA) under both conventional as well as microwave induced heating and some of them were screened against different fungal and bacterial strains.

Literature survey reveals the versatility of α,β-unsaturated ketones as a synthon in various heterocycles, and hence by using substituted 1,3-propanediones corresponding substituted chromones and acrylophenone derivatives were synthesized. The results of corresponding compounds are summarized in **Table1**. The structures of prepared novel compounds have been elucidated by chemical properties, spectroscopic data and elemental analyses.

EXPERIMENTAL SECTION

M.Ps. were measured in an open glass capillaries and are uncorrected. IR spectra in KBr were recorded on an instrument model spectrum one, serial number 68515 or Perkin Elmer – 577. ^{1}H NMR spectra were recorded on Varian mercury spectrometer YH-300,400 MHz and Brucker (400MHz) in $CDCl_3$ and DMSO-d6 by using TMS as an internal standard and chemical shifts are expressed in δ ppm. All reactions were monitored by TLC using silica gel 60-F 254 plates. The reactions were carried out in Scientific Microwave oven (scientific microwave system model–RG31L1, 700W, 2450 MHz). C,H,N analysis was carried out on Perkin-Elmer analyser. Purity of the sample has been checked on HPLC with LC-20 ATVP pumps, variable wave length programmable UV/VIS, detector SPD-10-AVP shimadzu and RP-C-18 column (250 mm x 46

mm). Mobile phase (methanol and water) was filtered through 0.2 µm membrane filter, and pumped from the solvent reservoir at the ratio 80: 20% volume by volume to the column at the rate of 1 ml/min. The volume of newly synthesized sample was 20 µl and then retention time was noted.

Synthesis of 1-(substitutedphenyl)-3-methyl-1,3 propanedione (2a-c)

General microwave procedure

To a mixture of substituted acetophenone (0.5gm) and ethylacetate (3ml), small pieces of metallic sodium (0.4gm) were added in small lots. Then the mixture was subjected to microwave irradiation for 1.5-2.5 min at power medium high. After cooling the reaction mixture was poured over crushed ice and acidified with glacial acetic acid, till it was acidic. Then crude products was filtered and washed with water and then crystallized from ethanol to get corresponding yield.

1-(2-Hydroxy-5-methylphenyl)-3-methyl 1,3-propanedione(2a): White crystalline solid, m.p. 102^0C, IR (KBr) : 3275 cm^{-1} (OH stret.), 1667 cm^{-1} (C=O stret.), 1617 cm^{-1} (C=C stret.). ^{1}H NMR (DMSO–d6): 2.30 (S, 3H, $ArCH_3$), 2.19 (S, 3H,O=C-CH_3), 4.1(S, 2H, O=C-CH_2-C=O), 6.30 (S, 1H, -C=CH), 6.8 – 7.5 (m, 3H, Ar-H), 11.80 (S, 1H, OH), 14.95 (S, 1H, =C-OH), 11.75 (S, 1H, OH) (Found: C=68.94, H=6.24, $C_{11}H_{12}O_3$ (192.20) requires C=68.74, H = 6.29%).

1-(2-Hydroxy-5-chlorophenyl)-3-methyl -1,3propanedione (2b): Yellowish crystalline solid, m.p. 112 ^{0}C, IR (KBr): 3421cm^{-1}(-OHstret.),1673cm^{-1} (C=O stret.), 1604 cm^{-1}(C=C stret.),797 cm^{-1} (C-Cl stret.). ^{1}H NMR (DMSO-d6): 2.40 (S, 3H, O=C-CH_3), 3.33 (S, 2H, O=C-CH_2-C=O), 6.30 (S, 1H,-C=C-H), 7.67-7.93 (m, 3H, Ar-H), 11.7 (S, 1H, ArOH). (Found: C=56.44, H=4.20, $C_{10}H_9ClO_3$ (212.63) requires C=56.48, H=4.26%)

Preparation of substituted chromones (3a-b)

General microwave procedure

A mixture of 1-(Substitutedphenyl)-3-methyl-1,3-propanedione(0.01mole) and polyphosphoric acid (PPA) (H_3PO_4 3ml and P_2O_5 4gm) was transferred to a reaction flask and was irradiated for 1hrs under microwave for 1-1.5min. After cooling the reaction mixture was poured into cold water (50ml). The crude product was filtered, washed and neutralized with minimum amount of base NH_3. Then crude product was recrystalized by ethanol to get corresponding yield.

2,6-Dimethylchromone(3a): White wooly solid, m.p. 107-109 ^{0}C, IR (KBr): 1641 cm^{-1}(-C=C stret.), 1352 cm^{-1} (γ-pyrone), ^{1}H NMR ($CDCl_3$): 2.43(S, 3H, $ArCH_3$), 2.36 (S, 3H, CH_3), 6.13 (S, 1H, =C-H), 7.25-7.94 (m,3H, Ar-H). (Found: C=75.83, H= 5.76, $C_{11}H_{10}O_2$ (174.20) requires C=75.84, H=5.78 %).

2-Methyl-6-chlorochromone(3b): yellowish wooly crystalline solid, m.p. 125-127 ^{0}C, IR (KBr): 1637 cm^{-1} (C=C stret.), 1350 cm^{-1} (γ-pyrone), ^{1}H NMR ($CDCl_3$): 2.9(S, 3H, $ArCH_3$), 6.8 (S, 1H, =C-H), 7.54-8.2 (m,3H, Ar-H). (Found: C=61.69, H= 3.25, $C_{10}H_7ClO_2$ (194.5) requires C=61.72, H=3.59 %).

Preparation of 1-(Substitutedphenyl)-2-(substitutedbenzylidene)-3-methyl-1,3-propane dione (4a-l).

General microwave procedure

A solution of 1-(Substituted phenyl)-3-methyl-1,3propanedione (0.01 mole) and aromatic aldehyde (0.015 mole) in ethanol (20ml) containing catalytic amount (0.005 mole) of TEBA was irradiated under microwave for 1.5-2 min. After cooling, the solid obtained was filtered, dried and recrystalised from ethanol to obtained corresponding yield.

1-(2'-Hydroxy-5'-methylphenyl)-2-benzyli dene-3-methyl-1,3-propanedione (4a):

Yellow crystalline solid, m.p. 70-72 ^{0}C, IR (KBr): 3530 cm^{-1} (-OH stret.), 1650 cm^{-1} (two-C=O stret.), 1550 cm^{-1} (C=C stret.), ^{1}H NMR ($CDCl_3$) : 2.05 (S, 3H, $COCH_3$), 2.27 (S, 3H, $ArCH_3$), 6.21 (s, 1H, =CH), 6.65-7.65 (m, 8H, ArH), 16.2 (s,1H, ArOH). (Found: C=77.10, H=5.67, $C_{18}H_{16}O_3$ (280.32) requires C=77.12, H= 5.75%).

1-(2'-Hydroxy-5'-chlorophenyl)-2-(2''-hydroxybenzylidene)-3-methyl-1,3-propanedione (4f):

Slightly yellowish, m.p.86-88 ^{0}C.IR (KBr): 3410 cm^{-1} (OH stret.), 3019 cm^{-1} (-CH stret.),1628 cm^{-1} (C=O stret.), 1559cm^{-1} (C=Cstret.), 1021 cm^{-1} (CH bending), 756 cm^{-1} (-C-Clstret.). ^{1}H NMR (DMSO-d6): 2.50 (S, 3H, $COCH_3$), 6.48 (S, 1H, C=CH), 6.85-7.94 (m, 7H, Ar-H), 10.2 (S, 1H,Ar-OH), 3.17 (S, 1H, OH), (Found: C= 64.32, H=4.11, $C_{17}H_{13}ClO_4$ (316.74) requires C=64.46, H=4.13%).

Evaluation of antimicrobial activity

Some newly synthesized active intermediates were screened for their antifungal and antibacterial activity against the fungi like *Aspergillus oryzae*, *Fusarium Oxysporum* and gram positive bacteria *staphylococci aureus* and Gram negative bacterial *E-Coli*. For the screening of antifungal and antibacterial activities, the disc diffusion method[28,29]was used. Nutrient agar (NA) was used as basal medium for test of bacteria and fungi respectively. Solutions having the concentration 100 ppm and 1000 ppm of the compound to be tested was prepared in DMF and 0.01 ml of solution was added to the wells made on the culture medium using an micropipette. The prepared plates were incubated at 37^{0}C for 24 hrs. The zone of inhibition around the well was checked and measured. Results are shown in **Table-2**.

RESULTS AND DISCUSSION

The compound 1-(2-Hydroxy-5-methylphenyl)-3-methyl-1,3-propanedione (2a) shows the IR absorption for OH stretching vibration at 3275 cm^{-1}, an carbonyl group stretching vibration at 1667 cm^{-1} and C=C stretching vibration at 1617 cm^{-1}. The ^{1}H NMR spectrum of (2a) exhibited a singlet of three protons of aromatic methyl group at 2.30, singlet of keto methyl group at 2.19, a singlet of $-CH_2$ observed at 4.1, multiplets in aromatic range are assigned for three protons at 6.8-7.5, and a sharp singlet at 11.75 due to OH proton. Similarly the structures of compounds (2b) and (2c) were confirmed on the basis of their spectral and elemental analyses.

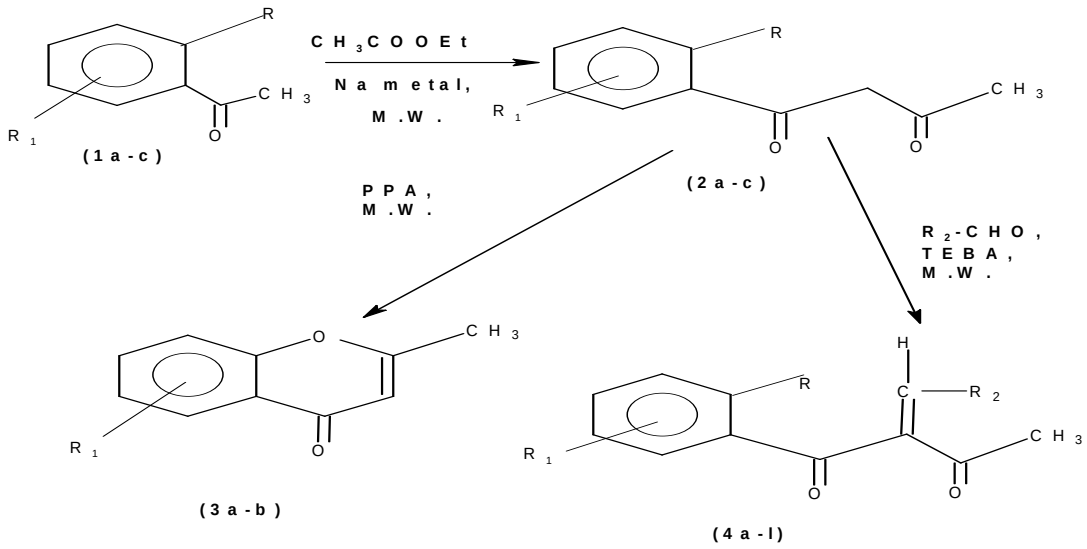
The compound 2,6-dimethyl chromone (3a) shows IR absorption for C=C stretching vibration at 1641 cm^{-1} and characteristic absorption at 1352 cm^{-1} due to γ - pyrone. ^{1}H NMR of compound (3a) exhibited a singlet of three aromatic protons at 2.43, a singlet of three protons of methyl group at 2.36, a sharp singlet of =C-H at 6.13, multiplates of three aromatic protons at

7.25-7.94 and broad peak of –OH group in compound (2a) get disappeared due to cyclization in compound (3a). Similarly the structures of compound (3b) was confirmed on the basis of its spectral and elemental analysis.

The compound 1-(2'-Hydroxy-5'-methylphenyl)-2-benzylidene-3-methyl-1,3-propane dione (4a) shows IR absorption at 3530 cm^{-1} due to –OH group, carbonyl peak at 1650 cm^{-1} and peak at 1550 cm^{-1} due to C=C stretching. ^1H NMR spectrum shows singlet at 2.05 due to three keto methyl protons, singlet of three aromatic protons at 2.27, singlet at 6.21 due to methyne proton, multiplates of eight protons at 6.65-7.65 and broad peak at 16.2 due to the aromatic –OH group . The compound 1-(2'-Hydroxy-5'-chlorophenyl)-2-(2''-hydroxybenzylidene)-3-methyl-1,3-propanedione (4f) shows sharp broad IR peak at 3410 cm^{-1} due to –OH group, IR absorption at 1628 and 1559cm^{-1} due to carbonyl group and C=C stret., and characteristics IR absorption at 756 cm^{-1} due to presence of C-Cl group. ^1H NMR shows deshielded singlet of three keto methyl protons at 2.50, two singlets at 10.2 and 3.16 due to presence of phenolic OH-groups, multiplates of seven protons observed at 6.85 – 7.94 and a sharp singlet of C=C-H at 6.48.

Biological evaluation of screened compounds showed moderate or maximum antibacterial and antifungal activities.In chromones, it was found that compound (3b) showed higher activity than compound (3a) for both fungi and bacteria. Both compounds had shown remarkable inhibitory activity against noted pathogens in higher concentration (1000ppm) than lower concentration (100ppm).

In acrylophenones, The compounds (4d), (4h), (4l) were found to. exhibit promising antifungal and antibacterial activities in both concentrations. The compound (4l) was strongly active towards *E-coli* in both concentrations. The compound (4b) was weakly active against *Aspergillus oryzae* in higher concentration while compound (4b) found to be inactive against *Aspergillus oryzae* in lower concentration.



R= H, OH, R_1= CH_3, Cl, NO_2, R_2= C_6H_5, 2-OH-C_6H_4, 4-OH-C_6H_4, 4NO_2-C_6H_4.

Table 1- Physical data of (2a-c), (3a-b), (4a-l)

Entry	R	R_1	R_2	Conventional Method (a)		Microwave Method(b)		M.P (^{0}C)
				Time (hrs)	Yield (%)	Time(min)	Yield (%)	
2a	OH	5-CH_3	-	1.5	75	1.5	83	102-104
2b	OH	5-Cl	-	1.5	73	1.5	84	112-114
2c	H	4-NO_2	-	2	70	2.0	81	176-178
3a	-	6-CH_3	-	0.5	75	1.0	80	107-109
3b	-	6-Cl	-	1	76	1.5	83	125-127
4a	OH	5-CH_3	C_6H_5	1	85	1.5	90	70-72
4b	OH	5-CH_3	2-OH-C_6H_4	1	86	1.5	92	98-100
4c	OH	5-CH_3	4-OH-C_6H_4	1	88	1.5	95	108-110
4d	OH	5-CH_3	4NO_2-C_6H_4	1.5	82	2.0	92	120-122
4e	OH	5-Cl	C_6H_5	1	83	1.5	90	92-94
4f	OH	5-Cl	2-OH-C_6H_4	1	85	1.5	92	86-88
4g	OH	5-Cl	4-OH-C_6H_4	1	83	1.5	93	77-78
4h	OH	5-Cl	4NO_2-C_6H_4	1.5	81	2.0	89	119-121
4i	H	4-NO_2	C_6H_5	1.5	80	1.5	86	109-111
4j	H	4-NO_2	2-OH-C_6H_4	1.5	82	2.0	89	115-117
4k	H	4-NO_2	4-OH-C_6H_4	1.5	83	2.0	85	122-124
4l	H	4-NO_2	4-NO_2-C_6H_4	2.0	78	2.0	83	135-137

Table 2-In vitro antifungal and antibacterial screening of some novel reactive intermediates

Sr.No.	Tested Compounds	Fungus (zone of inhibition in mm)				Bacteria (zone of inhibition in mm)			
		Aspergillus oryzae		*Fusarium oxysporum*		*E-coli* (Gram-ve)		*Staphylococci aureus* (Gram +ve)	
		100 ppm	1000 ppm	100 ppm	1000 ppm	100 ppm	1000 ppm	100 ppm	1000 ppm
1	3a	8	10	6	11	9	10	6	12
2	3b	10	12	8	13	12	14	11	14
3	4b	--	10	12	12	13	16	11	14
4	4d	16	18	20	21	18	22	14	18
5	4f	13	14	13	15	16	16	12	14
6	4h	19	22	21	22	24	25	20	23
7	4j	15	16	14	16	18	20	15	17
8	4l	19	20	23	24	26	27	22	25

'-' *No inhibition*

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