MICROWAVE ASSISTED SYNTHESIS AND ANTI MICROBIAL ACTIVITY OF 2,2-DIMETHYL CHROMENES

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Abstract: 2,2-Dimethyl chromenes (**1b-9b**) were prepared from corresponding propargyl ethers (**1a-9a**) under microwave conditions in high yields and anti microbial activity of compounds (**6b & 7b**) is reported.

Introduction :

2H-Chromenes are naturally occurring and biologically active heterocyclic compounds[1]. Natural 2,2-dimethyl-2H-chromenes are known to possess anti-juvenile hormone activity[2]. Chromenes are very important intermediates for the synthesis of flavonoids[3]. 6-Hydroxy-2,2-dimethyl chromene, a marine natural product was identified as an antioxidant and cancer protecting agent[4]. 7-Methoxy-2,2-dimethyl chromene (Precocene-I) and 6,7-dimethoxy-2,2-dimethyl chromene (Precocene-II) are reported to possess antiallototropic properties and induce precocious metamorphosis in several insects[5,2] and also known to have antihormonal activity[6], nematicidal[7], feeding deterrence[8] and anti microbial activity[9]. The isolated compound of 6-acetyl-2,2-dimethyl-1,2-benzopyran (Demethyl Encecalin) from receptacles of sunflower is shown to possess antimicrobial, antifungal[9] and plantgrowth inhibitor[10] activities. 6-Acetyl-7-methoxy-2,2-dimethyl benzopyran (Encecalin) has feeding deterrence and anti fungal activity[9]. Chromenes are also considered as important intermediates in the preparation of β-lapachones which are known to be potent inhibitors of DNA topoisomerase[11] and reverse transcriptase[12]. The importance of microwave assisted chromene synthesis is highly evident upon the perusal of the known methods of their synthesis in literature. The chromenes were prepared from propargylethers on heating with dimethylaniline[13] and clay[14]. Chromenes were also prepared by oxidative cyclisation of O-isoprenyl phenols[15], Lewis acid catalyzed reaction[16], palladium catalyzed reaction of 2-isoprenylphenols[17] and phenylboronic acid mediated synthesis[18]. Solid support reactions assisted by microwave are efficient, selective, solvent free and high yielding reactions[19].

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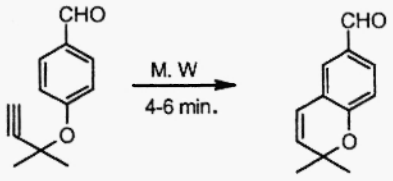
Results and Discussion :

Herein, we report the preparation of various bio-active chromenes (**1b-9b**) prepared from their corresponding propargylethers (**1a-9a, Scheme-1**) in high yields, among them the natural products synthesized are 2,2-dimethyl 2H-6-chromenyl methyl ether (**1b**), 2,2-dimethyl-2H-8-chromenyl methyl ether (**2b**), 1-(5-hydroxy-2,2-dimethyl-2H-6-chromenyl)-1-ethanone (**3b**), 2,2-dimethyl-2H-benzo[h] chromene (**4b**) and 3,3-dimethyl-2H-benzo[h]-chromene(**5b**).

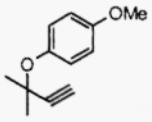
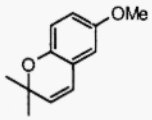
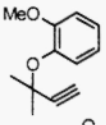
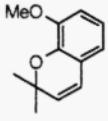
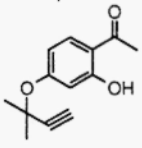
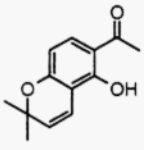
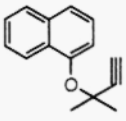
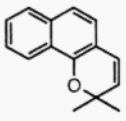
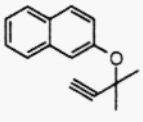
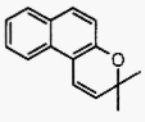
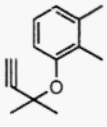
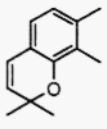
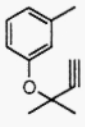
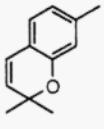
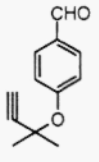
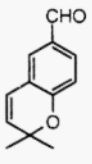
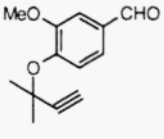
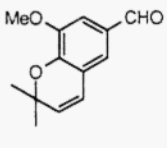


Scheme-1

The propargylethers[13] (**1a-9a**) were prepared by refluxing phenols in 10% aq. acetone with 2-chloro-2-methyl-but-3-yne in the presence of KI and K_2CO_3. The obtained propargyl ether (**1a**) was adsorbed on neutral alumina and subjected to microwave irradiation. The conversion of chromene (**1b**) was 45% in 2 min, 88% in 4 min and 94% in 6 min. The maximum conversion was 94% in 6 mins. The other propargylethers (**2a-9a**) under similar conditions afforded chromenes (**2b-9b**). The results obtained were tabulated in Table-1, clearly showing the efficient conversion of propargylethers to chromenes in good yields (**Table-1**). To show the acceleration in the rate of formation of chromenes due to microwave irradiation, under the same experimental conditions the propargylethers (**1a-9a**) were heated just by conventional heating. However, only low yields of products were obtained in longer reaction times. A maximum conversion of 88% was obtained even after 12hr. All the products were well characterized by ^{1}H NMR, IR and MS. It was observed that during the alkylation of α and β-naphthols (**Entry no. 4 & 5**), an in-situ cyclised product formation was noticed (10%). Our efforts towards making propargylethers of phenols in the presence of acid functionality on the ring were futile. It is important to note that the chromenes **6b** and **7b** are neither been isolated from any natural source nor are synthesized so far. The known compounds (**1a, 3a, 1b-5b, 8b & 9b** and unknown compounds (**2a, 4a-8a, 6b & 7b**) were well characterized by spectral data.

In conclusion, we are reporting the preparation and anti microbial activity of chromenes. We believe that the present method described here has definite use in organic synthesis due to its simplicity and efficiency. The yields of the products produced by microwave irradiation are high and the time required for conversion is very less.

Table-1

S. No.	Reactant (a)	Product (b)	Time (Min)	(%) Yeild
1			6	94
2			6	85
3			6	92
4			4	98
5			4	98
6			6	94
7			6	96
8			6	85
9			4	95

Experimental section:

^{1}H NMR spectra were obtained on a Varian 200 MHz spectrometer using $CDCl_3$ as solvent and TMS as internal standard. IR spectra were recorded on Nicollet spectrometer. Mass spectra were obtained on a VG micro mass 7070H instrument. The elemental analyses were carried out on Elementar vario EL instrument. The melting points were determined on Metler FPS instrument and are uncorrected.

General procedure:

The 1-(1,1-Dimethyl-2-propynyloxy-4-methoxy benzene (**1a**, 50mg), neutral alumina (250 mg) was mixed thoroughly in dichloromethane. After the solvent evaporation the substrate transferred into a glass test tube and placed in an alumina bath inside commercial microwave oven (BPL, BMO, 466 Watt) and irradiated for period of 4-6 min. The reaction was monitored by TLC, after completion of reaction (6min), the test tube was removed from the oven, allowed to attain room temperature and shaken with EtoAc (2x10 ml). The solvent was filtered, the filtrate was concentrated and the residue was purified by column chromatography over silica gel using EtOAc : hexane (20: 80) gave 2,2-dimethyl-2H-6-chromenyl methyl ether (**1b**) in 94 % yield.

Spectral Data :

1-(1,1-Dimethyl-2-propynyloxy)-2-methoxy benzene (2a) : Colorless liquid

IR ($CHCl_3$): 3295 , 1626, 1504, 1465, 1381, 1292 Cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.60 (s, 6H, $2CH_3$), 2.44 (s, 1H, CH), 3.84 (s, 3H, OMe), 6.82-6.94 (m, 2H, Aromatic), 7.14 (d, J = 3 Hz, 1H, Aromatic), 7.42 (d, J = 3 Hz, 1H, Aromatic). EI- MS (70 eV): *m/z* (%) = 190 (M^+, 40), 175 (100), 141 (30), 124 (40), 67(20), 41(20). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.41. Found: C, 75.73; H, 7.39.

1,1-Dimethyl-2-propynyl-1-naphthyl ether (4a) : Syrupy liquid.

IR ($CHCl_3$) : 3290, 1624, 1597, 1464, 1382, 1250, 1139 Cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.78 (s, 6H, $2CH_3$), 2.58 (s, 1H, CH), 7.36-7.6 (m, 5H, Aromatic), 7.76-7.82 (m, 1H, Aromatic), 8.18-8.28 (m, 1H, Aromatic). EI- MS (70 eV): *m/z* (%) = 211(M+1, (20), 196 (50), 145 (50), 123 (40), 77 (20). Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.65; H, 6.70.

1,1-Dimethyl-2-propynyl-2-naphthyl ether (5a): Colorless liquid.

IR ($CHCl_3$): 3294 , 1627, 1597, 1474, 1252 Cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.76 (s, 6H, $2CH_3$), 2.58 (s, 1H, CH), 7.30-7.48 (m, 3H, Aromatic), 7.62 (d, J =8.0 Hz, 1H, Aromatic), 7.75-7.82 (m, 3H, Aromatic). EI- MS (70 eV): *m/z* (%) = 210 (M^+, 30), 195 (100), 165 (30), 152 (25), 141 (20). Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.66; H, 6.69.

1-(1,1-Dimethyl-2-propynyloxy)-2,3-dimethyl benzene (6a): Colorless liquid

IR ($CHCl_3$): 3280, 1620, 1516, 1464, 1220, 1130, 918 Cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.74 (s, 6H, $2CH_3$), 2.2 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.58 (s, 1H, CH), 6.88 (d, *J* = 4 Hz, 1H, Aromatic), 7.10 (t, *J* = 7 Hz 1H, Aromatic), 7.40 (d, *J* = 6 Hz,1H, Aromatic). EI- MS (70 eV): *m/z* (%) = 188 (M^+,100), 174 (60), 160 (40), 142 (30), 133(20), 91(30), 77 (30). Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.56. Found: C, 82.92; H, 8.53.

2,2,7,8-Tetramethyl-2H-chromene (6b): Syrupy liquid

IR ($CHCl_3$): 1628, 1594, 1460, 1240, 1139, 970 Cm^{-1}.^1H NMR (200 MHz, $CDCl_3$): δ 1.42 (s, 6H, $2CH_3$), 2.10 (s, 3H, CH_3), 2.24 (s,3H,CH_3), 5.56 (d, *J* = 10 Hz, 1H, double bond), 6.28 (d, *J* = 10 Hz , 1H, double bond), 6.62 (d, *J* = 4 Hz, 1H, Aromatic), 7.38 (d, *J* = 6 Hz, 1H, Aromatic). EI- MS (70 eV): *m/z* (%) = 189 (M+1, 40), 175 (50), 161 (20), 91 (50). Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.56. Found: C, 82.91; H, 8.54.

1,1-Dimethyl-2-propynyl-3-methylphenyl ether (7a): Yellow syrupy liquid

IR ($CHCl_3$): 3292, 1642, 1611, 1502, 1464, 1230 Cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.62 (s, 6H, $2CH_3$), 2.56 (s, 1H, CH), 2.36 (s, 3H, CH_3), 6.84 (d, *J* = 4 Hz, 1H, Aromatic), 7.02 (s, 1H, Aromatic), 7.06 (d, *J* = 4Hz ,1H, Aromatic), 7.18 (d, *J* = 6 Hz, 1H, Aromatic). EI- MS (70 eV): *m/z* (%) = 174 (M^+,30), 159 (80),141 (40), 133 (50), 108 (60), 57 (100). Anal. Calcd for $C_{12}H_{14}O$: C, 82.71; H, 8.09. Found: C, 82.70; H, 8.07.

2,2,7-Trimethyl-2H-chromene (7b): Syrupy liquid.

IR ($CHCl_3$): 1615, 1506, 1464, 1420, 1220 1145, 980 Cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 6H, $2CH_3$), 2.24 (s, 3H, CH_3), 5.60 (d, *J* = 10 Hz, 1H, double bond), 6.42 (d, *J* =10 Hz,1H, double bond),6.54-6.62 (m, 2H, Aromatic), 6.96 (d,1H, Aromatic).EI-MS (70 eV): *m/z* (%) = 175 (M+1, 50), 156 (40), 136 (50), 91 (100). Anal. Calcd for $C_{12}H_{14}O$: C, 82.71; H, 8.09. Found: C, 82.69; H, 8.08.

4-(1,1-Dimethyl-2-propynyloxy)-3-methoxy benzaldehyde (9a): Solid, Mp: 58^{0}C

IR ($CHCl_3$): 2990, 2937 (H-C=O), 1688 (CHO),1585, 1462, 1268 Cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ 1.76 (s, 6H, $2CH_3$), 2.60 (s, 1H, CH), 3.86 (s, 3H, OMe), 7.38-7.40 (m, 2H, Aromatic), 7.62 (d, *J* = 10 Hz, 1H, Aromatic), 9.84 (s, 1H, -CHO). EI- MS (70 eV): *m/z* (%) = 218 (M^+,20), 153 (100), 142 (20), 95 (20). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.46. Found: C, 71.51; H, 6.44.

Anti bacterial assay of Compounds 6b and 7b:

Bacteria. Six test organisms, *Bacillus subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 96), *Pseudomonas aeruginosa* (MTCC 741), *Klebsiella aerogenes* (MTCC 39), *B. sphaericus* (MTCC 511), *Chromobacterium violaceum* (MTCC 2656) were obtained from the Institute of Microbial Technology, Chandigarh.

The ready made nutrient agar medium (23g) was dissolved in distilled water (1000ml) and heated to boiling until it dissolved completely. The medium and the Petri dishes were autoclaved at pressure of 15 lb/inc^2 for 20 min. stock solutions were prepared by dissolving plant extract in DMSO and different concentrations were made (**Table-2**) (30ug to 100ug).

Agar cup bioassay was employed for testing antibacterial activity of plant extract following the standard procedure (Linday, M. E, 1962). The medium was poured in to Petri dishes under aseptic conditions in a laminar flow chamber. When the medium in the

plates solidified, 0.5 ml of 24 h old culture of test organism was inoculated. After inoculation, cups were scooped out with 7mm sterile cork borer and the lids of the dishes

were replaced. To each cup different concentrations of test solutions (30, 100μg) were added. Controls were maintained with DMSO and penicillin G. The treated and the controls were kept in an incubator at 37°C for 24 hours . Inhibition zones were measured and diameter was calculated. Three to four replicates were maintained for each treatment.

Anti fungal assay of Compounds 6b and 7b:

Fungi.: Three test organisms *Rhizopus oryzae* (MTCC 262), *Aspergillus niger* (MTCC 281) and *Candida albicans* (MTCC 3017) were obtained from the Institute of Microbial Technology, Chandigarh.. The nutrient agar and the potato dextrose agar media were procured from M/S Himedia, Mumbai, India. The method followed for anti fungal bioassay is similar to that followed for anti bacterial assay where in the medium is potato dextrose agar and the control is Clotrimazole. Also, the treated and the controls were kept at RT for 48 hours and the standard employed is streptomycin (**Table-3**).

Acknowledgement

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Table-2: Anti bacterial activity levels of compounds 6b and 7b after 24 hours.

Microorganism **Gram +ve**	**Compound 6b** 30μg	100μg	**Compound 7b** 30μg	100μg	**Penicilin G** (30 μg)
B. subtilis	7	10	8	10	15
B. sphaericus	-	-	-	-	14
S. aureus	7	10	9	12	12
Gram -ve					**Streptomycin** (30μg)
P. aeruginosa	8	12	8	10	24
K. aerogenes	8	11	7	10	23
C. violaceum	-	-	-	-	24

Table-3: Anti fungal activity levels of compounds 6b and 7b after 48 hours.

Microorganism	**Compound 6b** 100μg	150μg	**Compound 7b** 100μg	150μg	**Control** **(Clotrimazole)** 100μg
Rhizopus oryzae	8	11	8	12	23
Aspergillus niger	7	10	7	10	26
Candida albicans	7	10	7	11	28

Inhibitory zone diameters are in mm.

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