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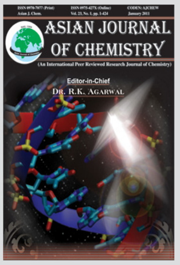

Comparative Study of Conventional and Microwave Assisted Synthesis of Chalcones

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An efficient, facile and eco-friendly microwave assisted approach for the synthesis of substituted chalcones by condensation of substituted acetophenones with substituted benzaldehyds in presence of an inorganic base is desired over time consuming convention synthesis method. The reaction time brought down from hours to seconds along with yield enhancement of substituted chalcones. The structures of synthesized chalcones have been established on the basis of their spectral data.

Key Words: Chalcone, Condensation, Microwave irradiation.

INTRODUCTION

In past few decades microwave-induced organic reaction enhancement (MORE) chemistry[1] gained popularity as a non-conventional technique for rapid organic synthesis[2]. Microwave technique is being implemented since 1970 due to the grater selectivity, enhanced reaction rate, cleaner product and manipulative simplicity[3,4]. It can be termed as 'e-chemistry' because it is easy, effective, economical and eco-friendly and is believed to be a step towards green chemistry. The most dramatic advantage is the speed with which reaction can be completed in minutes in microwave. Additional advantage include reduced solvent usage (an important environmental consideration and a source of substantial cost saving) and significant increase in yield as well as higher product purity due to decreased formation of by-products. Chalcones[5,6] (Fig. 1) constitute an important class of naturally occurring compound which finds use as intermediates in the synthesis of biologically active molecules such as pyrazolines[7], thiophene[8], aurones[9], coumarins[10], furan[11], oxazines[12], quinoxalines[13], isoxazolines[14], benzothiazepines[15], pyrimidinones[16], pyrazoles[17]. The chalcones and their analogues exhibit various biological activities such as antibacterial[18], larvicidal[19], antiinflammatory[20], antimalarial[21], anticancer[22] and antimycobacterial[23,24]. The diversity of biological application has been suggested due to the presence of ketovinyl group (-CH=CH-CO-) which react with thiol group of essential enzymes.

A number of conventional methods have been employed for the synthesis of chalcones which take longer heating time and poor yield and require appreciable amount of solvent. Therefore a simple facile, environmental friendly, non-conventional approach has been developed in present work for the synthesis of chalcones using house hold microwave oven and compared the percentage yield and time require for completion of reaction by using conventional method and microwave method.

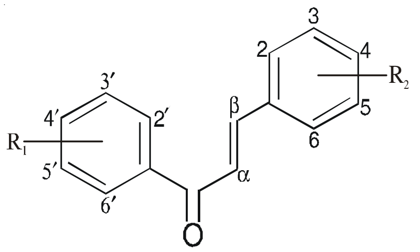

Fig. 1. Structure of chalcone molecule

EXPERIMENTAL

The substituted acetophenones (4-hydroxy, 3-nitro, 4-nitro, 4-amino) and substituted benzaldehydes (4-hydroxy, 4-hydroxy-3-methoxy, 4-dimethylamino, 2-chloro) were employed for the synthesis of chalcones. Melting points were determined in Thomas Hoover melting point apparatus and are uncorrected. UV spectra were taken by using Perkin-Elmer Lambda 15 UV/Vis spectrometer. IR spectra of the corresponding compounds were recorded on a Shimadzu 8201 PC spectrometer (4000-400 cm^{-1}) by using KBr palates and absorption bands are reported in cm^{-1}. The ^1H NMR spectra were recorded on Bruker DRX-300 (300 MHz FT NMR) spectrometer in deutreted methanol using TMS as internal standard and chemical shift are expressed in δ (ppm) values. The FAB mass spectra were recorded on a JEOL S X 102 mass spectrometer using Argon/Xenon (6 KV, 100 mA) as the FAB gas. All reactions were monitored by thin layer chromatography carried out on 0.2 mm silica gel G plats using suitable solvent systems. The purity of the compounds was ascertained by thin layer chromatography as well as preparative TLC using suitable solvent system. Samsung G2739N microwave oven (20 L capacity, 2450 MHz, 1500 W) has been used in synthesis of compounds. All the chemicals used were obtained from E-merck/ Glaxo Ltd, Mumbai. The reagents and solvents such as hexane, benzene, chloroform, acetone, ethanol and methanol used were of LR and AR grade.

Synthesis of substituted chalcones

By conventional method: A mixture of substituted acetophenone (0.1 mol) and substituted benzaldehyde (0.1 mol) dissolved in 250 mL of ethanol was taken in a round bottom flask, kept in ice bath. The condensation was affected by adding of a strong solution of KOH (75 mL, 12 N) drop by drop using constant stirring. The reaction mixture was left in the same ice bath for 0.5 h and then refluxed for 9-12 h. The completion of reaction was monitored by using silica gel thin layer chromatography (TLC) plates using mobile phase. The resultant mixture was cooled, neutralized with ice cold dilute HCl (5 %), stirred, when precipitate of crude substituted chalcone obtained which was filtered, washed thoroughly with ice cold distilled water, till free from acid[25,26]. The crude chalcone was purified and crystallized from methanol.

By microwave assisted method: The condensation of substituted acetophenone (0.1 mol) with substituted benzaldehyde (0.1 mol) was carried out using ethanol as energy transfer medium in the presence of base (KOH) in the specially designed conical flask fitted with calcium chloride guard tube to absorb solvent vapours for 10 to 50 s at 450 watts microwave power. The progress of the reaction was monitored by silica gel thin layer plates using chloroform:acetone (8:2) solvent systems as well as by the appearance of coloured product during reaction. After completion of reaction, the work up of the product was carried out according to the procedure similar to conventional method. A comparative study of reaction time and yield of all chalcones prepared by conventional method (CM) as well as microwave assisted method (MwAM) shown in Table-1.

By adopting the above mentioned conventional and microwave methods the following eight chalcones were synthesized: 4,4′-dihydroxychalcone (**C-1**), 4,4′-dihydroxy-3-methoxychalcone (**C-2**), 2-chloro-4′-hydroxychalcone (**C-3**), 4-dimethylamino-4′-nitrochalcone (**C-4**), 4′-amino-4-hydroxychalcone (**C-5**), 4-amino-2-chlorochalcone (**C-6**), 4-hydroxy-3′-nitrochalcone (**C-7**) and 4-dimethylamino-3′-nitrochalcone (**C-8**).

RESULTS AND DISCUSSION

All the eight chalcones synthesized by conventional method as well as a rapid and efficient microwave assisted method showed characteristic colour reactions of chalcones. From Table-1 it is evident that microwave assisted synthesis of chalcones proceed quickly with very good yield and crude product is cleaner as compared to conventional method which is time consuming, gives low yield and requires an appreciable amount of solvents. The resulting compounds were characterized by UV-Vis, IR and ^{1}H NMR and mass spectra as follow:

4,4′-Dihydroxychalcone (C-1): m.p. 130 ºC; UV-vis (MeOH) λ_{max}: 223, 345 nm; IR (KBr, ν_{max}, cm^{-1}): 3215 (OH), 1642 (CO-CH=CH); ^{1}H NMR (CD_3OD, 300 MHz) δ: 7.56 (d, 1H, H_α), 8.00 (d, 1H, H_β); FAB-MS at m/z 240 [M^+], 239 [M^+-1], 212, 147, 121, 119, 107, 77.

4,4′-Dihydroxy-3-methoxychalcone (C-2): m.p. 180 ºC; UV-Vis (MeOH) λ_{max}: 232, 320, 357 nm; IR (KBr, ν_{max}, cm^{-1}): 3167 (OH), 2827 (OCH_3), 1638 (CO-CH=CH); ^{1}H NMR (CD_3OD, 300 MHz) δ: 3.95 (s, 3H, -OCH_3), 7.22 (d, 1H, H_α), 8.05 (d, 1H, H_β); FAB-MS at m/z 270 [M^+], 269 [M^+-1], 177, 149, 137, 121, 77.

2-Chloro-4′-hydroxychalcone (C-3): m.p. 70 ºC; UV-vis (MeOH) λ_{max}: 265, 390 nm; IR (KBr, ν_{max}, cm^{-1}): 3208 (OH), 1643 (CO-CH=CH), 1053, 760 (*o*-chloro substitute); ^{1}H NMR (CD_3OD, 300 MHz) δ: 7.25 (d, 1H, H_α), 7.41 (d, 1H, H_β, d); FAB-MS at m/z 258 [M^+], 259 [M^++1], 165, 137, 125, 119, 77.

4-Dimethylamino-4′-nitrochalcone (C-4): m.p. 160 ºC; UV-vis (MeOH) λ_{max}: 249, 320, 354 nm; IR (KBr, ν_{max}, cm^{-1}): 2805 ($N(CH_3)_2$ str.), 1690 (CO-CH=CH), 1430 (CH deformation in -NCH_3), 1339 (*ter.* amine NCH_3 str.) 1546, 1322, 1174, 521 (NO_2 asymm. str., symm. str., C-N str. and in plane NO_2 bend.); ^{1}H NMR (CD_3OD, 300 MHz) δ: 3.33 (s, 6H, -$N(CH_3)_2$) 7.58 (d,1H, H_α), 8.03 (d, 1H, H_β); FAB-MS at m/z 296 [M^+], 295 [M^+-1], 268, 174, 150, 146, 134, 77.

TABLE-1
COMPARISON OF REACTION TIME AND YIELD OF CHALCONES PREPARED BY CONVENTIONAL METHOD (CM) AND MICROWAVE ASSISTED METHOD (MwAM)

Chalcone	R_1	R_2	m.p. (ºC)	Colour	Reaction time		Yield (%)	
					CM (h)	MwAM (s)	CM	MwAM
C-1	4'-OH	4-OH	130	Lemon yellow	15	30	55	85
C-2	4'-OH	4-OH-3-OCH_3	180	Orange	15	50	54	80
C-3	4'-OH	2-Cl	70	White	10	28	75	85
C- 4	4'-NO_2	4-$N(CH_3)_2$	160	Yellow	11	15	72	88
C-5	4'-NH_2	4-OH	98	Orange	8	20	68	80
C-6	4'-NH_2	2-Cl	74	Cream	10	36	68	82
C-7	3'-NO_2	4-OH	185	Yellow	11	20	66	84
C-8	3'-NO_2	4-$N(CH_3)_2$	110	Coffee	9	30	70	90

All melting points are incorrect.

4′-Amino-4-hydroxychalcone (C-5): m.p. 98 ºC; UV-vis (MeOH) λ_{max}: 224, 328, 367 nm; IR (KBr, ν_{max}, cm^{-1}): 3408 (NH_2), 3245 (OH), 1648 (CO-CH=CH), 1035 (CN); ^{1}H NMR (CD_3OD, 300 MHz) δ: 3.33 (s, 2H, -NH_2), 7.26 (d, 1H, H_α), 7.72 (d, 1H, H_β), 9.79 (s, 1H, -OH); FAB-MS at m/z 239 [M^+], 238 [M^+-1], 211, 147, 120, 119, 107, 77.

4′-Amino-2-chlorochalcone (C-6): m.p. 74 ºC; UV-vis (MeOH) λ_{max}: 262, 314, 390 nm; IR (KBr, ν_{max}, cm^{-1}): 3413 (NH_2), 1703 (CO-CH=CH), 1324 (aromatic ring C-N str.), 1052, 749 (*o*-chloro substituted); ^{1}H NMR (CD_3OD, 300 MHz) δ: 3.78 (s, 2H, -NH_2), 7.25 (d, 1H, H_α), 7.42 (d, 1H, H_β); FAB-MS at m/z 257 [M^+], 258 [M^++1], 228, 165, 137, 125, 120, 77.

4-Hydroxy-3′-nitrochalcone (C-7): m.p. 185 ºC; UV-vis (MeOH) λ_{max}: 270, 353, 322 nm; IR (KBr, ν_{max}, cm^{-1}): 3167, 1691 (OH), 1444, 1322, 1166 (NO_2 symm. str., assym str., C-N str.); ^{1}H NMR (CD_3OD, 300 MHz) δ: 7.42 (d, 1H, H_α), 7.81 (d, 1H, H_β), 9.79 (s, 1H, -OH); FAB-MS at m/z 269 [M^+], 268 [M^+-1], 241, 150, 147, 119, 107, 77.

4-Dimethylamino-3′-nitrochalcone (C-8): m.p. 110 ºC; UV-vis (MeOH) λ_{max}: 290, 348 nm; IR (KBr, ν_{max}, cm^{-1}): 2824 ($N(CH_3)_2$ str.), 1686 (CO-CH=CH), 1547, 1325 (NO_2 asymm. str., symm. str.), 1439 (CH deformation in NCH_3),1356 (*ter.* amine NCH_3 str.); ^{1}H NMR (CD_3OD, 300 MHz) δ: 3.32 (s, 6H, -$N(CH_3)_2$), 7.66 (d,1H, H_α), 8.76 (d, 1H, H_β); FAB-MS at m/z 296 [M^+], 295 [M^+-1], 268, 174, 150, 146, 134, 77.

From the spectral data, it is evident that all the chalcones showed the presence of ketovinyl group (-CO-CH=CH-) in the range of 1639 to 1690 cm^{-1}, the presence of -OH, -OCH_3, -NO_2, -NH_2 and -N $(CH_3)_2$ were also characterized by IR spectrum. ^{1}H NMR spectrum showed a pair of doublet corresponding to vinylic H_α and H_β protons in the range of 7.20 to 8.12 ppm and 7.52 to 8.33 ppm, respectively. All the chalcones showed strong mass peak followed by [M-1] peak or [M+1] peak.

Conclusion

An eco-friendly more convenient microwave assisted synthesis of bioactive chalcones has been developed. Compare to conventional condensation this methodology saves significant time and very often improves yields of substituted chalcones.

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