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Microwave Mediated Synthesis and Characterization of Bioactive Flavones Through Chalcone and Comparative Study with Conventional Method

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Abstract

Treatment of different substituted aromatic aldehydes **(a-b)** with 2-hydroxy acetophenone in basic medium (NaOH/KOH) under microwave (MW) conditions afforded corresponding chalcones through Claisen-Schmidt condensation process. These intermediate compounds **(2a-b)** were cyclized in presence of I_2/DMSO/H_2SO_4 to obtain flavones **(3a-b)** by means of intramolecular cyclization process. The structure of this synthesized compound was confirmed by using ^{1}H-NMR, ^{13}C-NMR, IR and UV analysis and the yield was fairly good. These synthesized compounds showed a good range of antimicrobial potency.

Keywords: Aldehyde, Acetophenon, Chalcone, Cyclization, Claisen- Schmidt condensation, DMSO, Flavone.

Introduction

Flavonoids consist of a large group of polyphenolic compounds having a benzo-γ-pyrone structure and are ubiquitously present in plants. Available reports tend to show that secondary metabolites of phenolic nature including flavones are responsible for the variety of pharmacological activities [1, 2].The chemical nature of flavones depends on their structural class, degree of hydroxylation, other substitutions and conjugations, and degree of polymerization [3]. Recent interest in these substances has been stimulated by the potential health benefits arising from the antioxidant, anticancer antifungal activities and anti–human immunodeficiency virus functions[4] of these polyphenolic compounds. Functional hydroxyl groups in flavones mediate their antioxidant effects by scavenging free radicals and/or by chelating metal ions [5, 6]. The chelation of metals could be crucial in the prevention of radical generation which damage target biomolecules [7, 8]. By using MW method in this synthesis, it would be able to achieve very high regioselectivity compared to the results obtained under conventional heating method. MW-assisted oxidative rearrangement

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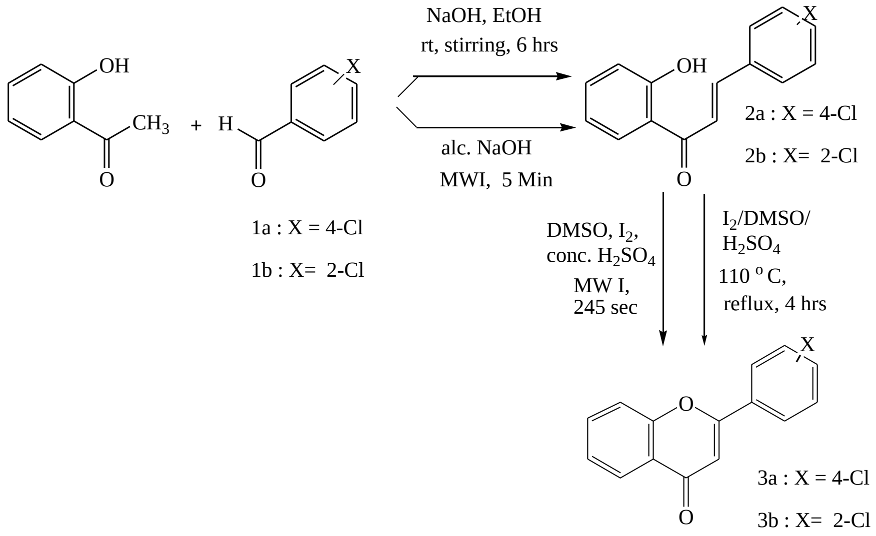
of chalcones to flavones was carried out in better yield with eco-friendly reagent of hypervalent iodine instead of thallium nitrate (TTN), a toxic, environmentally unfriendly, and expensive reagent [9]. An eco-friendly synthetic approach to synthesize bioactive molecules under microwave condition also led to large diminutions of reaction times, better yielding, and overall the need for less solvents protocol that upholds the concepts for sustainable and green chemistry as well.

Experimental Section

The melting point of the synthesized compounds was taken on a Fisher-John's electro-thermal melting point apparatus by thin disc method and was not corrected. IR spectra were obtained on FT / IR-plus (shimadzu) spectrophotometer using KBr pellets. ^{1}H-NMR spectra was recorded using 400 MHz, Bruker NMR spectrometer using TMS (tetra methyl silane) as the internal standard. Deutarated solvents such as chloroform ($CDCl_3$) and dimethyl sulfoxide (DMSO-d_6) were used as solvents.



Scheme: 1

Synthesis of 1-(2'-hydroxy-phenyl)-3-(4"-chloro-phenyl)-propenone (2a):

Microwave mediated method: A solution of NaOH (2.10 g, 0.053mol) in a mixture of 15 mL of water and 10 mL of ethanol was prepared. Then 2'-

hydroxyacetophenone (1.74 g, 0.0125 mol) and 4’’-chlorobenzaldehyde (1a), (1.78 g, 0.0125 mol) were added. The resulting solution was irradiated under MW for about 5 min (30 sec × 10 times, 1-2 min interval/irradiation) (scheme 1). The completion of the reaction was monitored by TLC using EtOAc: n-hexane. After completion, the mixture was neutralized with dilute HCl. A solid mass obtained was filtered off and purified by recrystallization from a mixture of ethyl acetate and n-hexane. Finally the titled compound (2a) was obtained as a yellow solid.

CH method: A solution of NaOH (2.10 g, 0.053 mol) in a mixture of 13 mL of water and 25 mL of ethanol was prepared. Then 2'-hydroxyacetophenone (1.74 g, 0.0125 mol) and 4’’-chloro benzaldehyde (1.78 g, 0.0125mol) were added. The resulting solution was stirred at room temperature for about 6 hrs (scheme 1). The completion of the reaction was monitored by TLC using EtOAc: n-hexane. After completion of the reaction the mixture was neutralized with dilute HCl. A solid mass obtained was filtered off and purified by recrystallization from a mixture of ethyl acetate and n-hexane. Finally the titled compound (2a) was obtained as a yellow solid.

Melting point: 155^{o}C - 157^{o}C & UV λ_{max} (log ε) (MeOH): 319 (0.410).

Yield: 97 %, (3.62g) (MW) & 90% (3.01g) (CH)

IR (KBr) υ (cm^{-1}): 3428 (s, br, O-H, stretch); 3059 (Ar, C-H, stretch);1639 (s, C=O, keto); 1564 (s, C=C, alkene); 1486 (s, C=C, Ar); 1205 (s, C-O, stretch); 1159 (s, C-C, stretch);785 (s, C-Cl, stretch). **^{1}H-NMR (CDCl$_3$) δ_H (ppm):** 12.76 (s, 1H, Ar-OH); 7.94 (dd, 1H, J_o = 8.4 Hz, J_m= 1.6 Hz, Ar-$H_{6'}$); 7.89 (d, 1H, J_{trans}= 15.6 Hz, =C-H_b); 7.65 (d, 1H, J_{trans}= 15.6 Hz, =C-H_a); 7.62 (d, 2H, J_o= 8.4 Hz, Ar-$H_{2', 6''}$); 7.56 – 7.52 (m, 1H, Ar-$H_{4'}$); 7.44 (d, 2H, J_o= 8.4 Hz, Ar-$H_{3'', 5''}$); 7.06 (d, 1H,J_o= 8.4 Hz, Ar-$H_{3'}$); 6.99 – 6.97 (m, 1H, Ar-$H_{5'}$). **^{13}C-NMR (CDCl$_3$) δ_C (ppm):** 192.68 (C=O), 122.38 (=C_α), 144.67 (=C_β), 163.86 (C_{OH}), 118.73, 119.01, 119.99, 125.16 and 129.00 (aromatic carbons)

Synthesis of 2-(4'-chloro-phenyl)-chromen-4-one (3a):

Microwave mediated method: Compound 2a (0.506 g, 1.78 mmol) was dissolved in 6 mL DMSO with 3-4 drops of conc. sulfuric acid and iodine

(10 mole %). Then the mixture was irradiated under MW for 245 second (scheme 1). The completion of reaction was monitored by TLC using ethyl acetate: n-hexane. After addition of water, the resulting precipitate was collected by filtration and washed with aqueous 20% sodium thiosulphate and water. The dried solid mass was recrystallized from a mixture of ethyl acetate and n-hexane and an off white fluffy crystalline solid was obtained.

CH method: Compound 2a (0.506 g, 1.78 mmol) was dissolved in 10 mL of DMSO and 3-4 drops of conc. sulfuric acid was added. After 15 min of stirring, I_2 (10 mol %) was added and refluxed at 110^{o}C for about 4 hrs (scheme 1). The completion of reaction was monitored by TLC using ethyl acetate: n-hexane. The precipitate was collected by filtration and washed with aqueous 20% sodium thiosulphate and water. The crude solid mass was recrystallized from a mixture of ethyl acetate and n-hexane and off white fluffy crystalline solid was obtained.

Melting point: 206^{o}C- 208^{o}C & UV λ_{max} (log ε) (MeOH): 298.50 (0.382).

Yield: 74% (0.59g) (MW) & 70% (0.35 g) (CH).

IR (KBr) υ (cm^{-1}): 3071 (C-H, Ar, stretch)**;** 1640 (s, C=O, keto); 1573 (s, C=C, alkene); 1467 (s, C=C, Ar). **^{1}H-NMR (CDCl$_3$) δ_H (ppm):** 8.26 (dd, 1H, J_o = 8.0 Hz, J_m= 1.6 Hz, Ar-H$_5$); 7.90 (d, 2H, J_o= 8.4 Hz, Ar-H$_{2', 6'}$); 7.76 - 7.72 (m, 1H, Ar-H$_6$); 7.59 (d, 1H, J_o = 8.4 Hz, Ar-H$_8$); 7.53 (d, 2H, J_o= 8.4 Hz, Ar-H$_{3', 5'}$); 7.48 - 7.44 (m, 1H, Ar-H$_7$); 6.83 (s, 1H, H$_3$). **^{13}C-NMR (CDCl$_3$) δ_C (ppm):** 178.27 (C=O), 162.26 (C$_2$, vinylic carbon), 107.70 (C$_3$, vinylic carbon), 156.16 (C$_9$), 137.92 (C$_{1'}$), 133.94 (C$_7$), 130.27 (C$_{4'}$), 129.40 (C$_{2',6'}$), 127.56 (C$_{3', 5'}$), 125.77 (C$_6$), 125.40 (C$_5$), 123.92 (C$_{10}$), 118.05 (C$_8$).

Synthesis of 1-(2'-hydroxy-phenyl)-3-(2-chloro-phenyl)-propenone (2b):

Similar treatment of compound 1b (1.78 g, 0.0125 mol) and 2'-hydroxyacetophenone (1.74 g, 0.0125 mol) with a mixture of aqueous and alcoholic solvent in basic medium, resulting a yellow solid compound after completion and the yield was 90% (2.97g) (MW) and 85% (2.80g) (CH).

Melting point: 109^{o}C – 111^{o}C & UV λ_{max} (log ε) (MeOH): 308.50 (0.334).

IR (KBr) υ (cm^{-1}): 3482 (s, br, O-H, stretch); 3065 (C-H, Ar, stretch)**;** 1641 (s, C=O, keto); 1585 (s, C=C, alkene); 1486 (s, C=C, Ar); stretch). **^{1}H-NMR ($CDCl_3$) δ_H (ppm):**12.73 (s, 1H, Ar-OH); 8.33 (d, 1H, J_{trans}= 15.6 Hz, =C-H_b);) 7.93 (dd, 1H, J_o = 8.0 Hz, J_m= 1.2 Hz, Ar-$H_{6'}$); 7.79 (dd, 1H, J_o = 7.6 Hz, J_m= 1.2 Hz, Ar-H_6); 7.67 (d, 1H, J_{trans} = 15.6 Hz, =C-H_a); 7.56-7.48 (m, 2H, Ar-$H_{4',3}$); 7.41-7.35 (m, 2H, Ar-$H_{4,5}$); 7.06 (d, 1H, J_o = 8.0 Hz, Ar-$H_{3'}$); 6.99-6.95 (m, 1H, Ar-$H_{5'}$) **^{13}C-NMR ($CDCl_3$) δ_C (ppm):** 190.68 (C=O), 118.38 (=C_a), 141.67 (=C_b), 162.86 (C_{OH}), 122.53, 116.35, 135.86, 122.37, 133.3, 133.1, 131.2, 128.50, 129.65, 127.8, 126.21 and 121.9 (aromatic carbon)

Synthesis of 2-(2'-chloro-phenyl) - chromen-4-one (3b):

Similar treatment with compound 2b (0.506 g, 1.78 mmol) was carried out with DMSO and 3-4 drops of conc. sulfuric acid in presence of I_2 (10 mol %) (Scheme 1). The completion of reaction was monitored by TLC and an off white fluffy crystalline solid was obtained having yield of 75% (0.35g) (MW) and 70% (0.32g) (CH).

Melting point: 210^{o}C - 212^{o}C & UV λ_{max} (log ε) (MeOH): 279 (0.096); 243 (0.163).

IR (KBr) υ (cm^{-1}): 3049 (C-H, Ar, stretch)**;** 1631 (s, C=O, keto); 1593 (s, C=C, alkene); 1554 (s, C=C, Ar). **^{1}H-NMR ($CDCl_3$) δ_H (ppm):** 8.24 (dd, 1H, J_o = 7.6 Hz, J_m= 1.6 Hz, Ar-H_5); 8.17 (dd, 1H, J_o = 7.6 Hz, J_m= 1.6 Hz, Ar-H_8); 7.83 (dd, 1H, J_o = 7.2 Hz, J_m= 1.6 Hz, Ar-$H_{6'}$); 7.60-7.46 (m, 4H, Ar-$H_{3',4;5',7}$); 7.22 (t, 1H, J_o = 7.6 Hz & J_o= 8 Hz, Ar-H_6); 6.84 (s, 1H, H_3). **^{13}C-NMR ($CDCl_3$) δ_C (ppm):** 177.07 (C=O), 161.66 (C_2), 106.80 (C_3); 155.16, 136.92, 134.94, 131.27, 128.40, 126.56, 124.77, 124.40 and 118.55 (aromatic carbon).

Result and Discussion

A crucial MW assisted treatment of substituted benzaldehydes (3a-b) with 2-hydroxy acetophenone had been carried out in basic medium with solvent of water and ethanol gave the titled yellow solid compound (2a-b).The subsequent MW mediated cyclization of solid chalcone (2a-b) in presence of $DMSO/H_2SO_4$ with 10% I_2 gave desired crystalline solid of flavones (3a-b) with 74% yield. In comparison with conventional heating method the solvent and reagent ratio in both two steps (Scheme 1) are less in quantity under MW condition. In case of percentage of yield the conventional method had almost about 80% and 60% product for chalcones (2a-b) and flavones (3a-b) respectively which was also less in amount. Time consumed for CH method had taken several hrs in both steps to obtain 2a-b/3a-b under reflux condition whereas MW only took few minutes/seconds.

The spectral data of synthesized compound chalcones (2a-b) and flavones (3a-b) was confirmed through IR, ^{1}H-NMR, ^{13}C-NMR and UV analysis.

In IR analysis of compound (2a-b), the distinctive strong and broad absorption band was found at 3428 cm^{-1} due to the presence of O-H group. The aromatic/vinylic group showed at 3059 cm^{-1} and conjugated C=O bond at 1639 cm^{-1}. The bands at 1564 cm^{-1} and 1486 cm^{-1} were due to the C=C bond. The band at 785 cm^{-1} was due to the presence of C-Cl bond. In ^{1}H-NMR analysis, chalcones have ethylenic protons nearer the carbonyl group are called as Ha protons and Hb protons (Figure 1). Ha protons of chalcones showed chemical shift at upfield than those of Hb protons. This is possibly due to the polarization of the C=C double bond in the system being predominantly caused by the carbonyl group so as to make electron density at "a" position than at "b" position. Due to the anisotropic effect, the protons on two phenyl rings give chemical shift greater than expected. In the ^{1}H-NMR spectrum of 2'-hydroxy chalcones (2a-b), hydroxyl proton appears at δ_H = 12.76 ppm. The high frequency resonances of these protons are due to the intramolecular hydrogen bond formed with the carbonyl group. The vinylic protons appear as doublets at Ha=7.65 ppm and Hb=7.89 ppm.

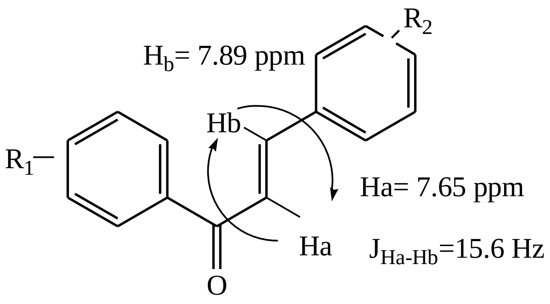


Figure 1: General presentation of chalcone protons having enone structure

If the coupling constants value shows $J_{Ha\text{-}Hb}$=8 Hz, that indicates cis configuration of vinylic system .But as the coupling constants value of compound 2a-b was $J_{Ha\ \text{-}Hb}$=15.6 Hz, that points out specifically trans configuration of vinylic system. In ^{13}C-NMR spectrum of chalcones (2a-b), the carbonyl carbon appeared at δ192.68 and α and β-carbon atoms with respect to the carbonyl group gave characteristic signals at δ122.38.1 ppm and δ144.67 ppm respectively. The carbon atom attached with a hydroxyl group gave a peak at δ163.86 ppm.

The spectral data of one of the synthesized flavone is explained for supporting the structural identification. In IR analysis of compound 3a-b, the above compound showed a strong absorption band at 3071 cm^{-1} due to the presence of aromatic/vinylic C-H bond. A strong absorption band at 1640 cm^{-1} indicated the presence of conjugated C=O bond and at 1573 cm^{-1} the C=C alkene bond. The bands at 1467 cm^{-1} was due to the C=C bond for aromatic compound.

In ^{1}H-NMR analysis, compound 3a-b showed specific singlet at δ_H = 6.83 ppm. This indicated the single hydrogen attached to C-3 carbon that resembles the characteristics of specific proton of flavones. The others proton have also given their identical peak with similar position. In the ^{13}C NMR spectrum, the most downfield shifted peak was 178.27 ppm which one assigned ketone group (C-4).The next downfield shifted peak 162.26 ppm was C-2 and C-3 was comparatively at upfield at 107.70 ppm and other aromatic carbon gave their respective peaks as well.

The subsequent study of the interaction of the said class of compounds is of great interest, in particular, to look at the synergistic/additive or antagonistic effects in cancer cell lines in the next phase [9-10]. This has great significance clinically as mostly patients are taking synthetic drugs besides natural compounds to aid their fight against cancer [10-11]. This proposal is also deals with Green Chemistry and Sustainable Development due to adopting superior methods, a prime environmental issue, to protect our planet from hazards posed by classical chemistry practice [11]. Therefore, this research will definitely play a vital role in the development of the field of Medicinal Chemistry in worldwide for understanding human health and disease.

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