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Research Article

SYNTHESIS OF FLAVONES FROM 2-HYDROXY ACETOPHENONE AND AROMATIC ALDEHYDE DERIVATIVES BY CONVENTIONAL METHODS AND GREEN CHEMISTRY APPROACH

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ABSTRACT

Objective: Flavones occupy a special place in the realm of natural and synthetic organic chemistry owing to their diversified biological activities. In this study, a series of chalcone derivatives were synthesized and after cyclization of chalcone to synthesized various substituted flavone derivatives (2A-2L).

Methods: The reaction of 2-hydroxy acetophenone with substituted aromatic aldehydes produced chalcone by trituration (NaOH) and conventional methods (KOH/EtOH), which upon further cyclization with dimethyl sulfoxide/I_2 resulted to form flavone derivatives.

Results: The purity of compounds was ascertained by melting point and thin-layer chromatography. The synthesized compounds have been characterized by mass, infrared, and ^{1}H nuclear magnetic resonance spectral analysis.

Conclusion: Based on spectral data, it was proved that all synthesized chalcones and flavones derivatives meet the standard values of various spectral techniques and further it will be evaluated for pharmacological activities.

Keywords: Chalcone, Flavone, Trituration, Conventional, Claisen-Schmidt condensation.

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INTRODUCTION

Flavonoids are a group of more than 4000 polyphenolic compounds that occur naturally in foods of plant origin. These compounds possess a common phenylbenzopyrone structure (C6-C3-C6), and they are categorized according to the saturation level and opening of the central pyran ring, mainly into flavones, flavanols, isoflavones, flavonols, flavanones, and flavanonols [1,2]. Flavones occupy a special place in the realm of natural and synthetic organic chemistry owing to their useful biological activities such as antioxidant [3-7], anxiolytic [8], anticancer [9-11], analgesic and anti-inflammatory [12-14], antimicrobial [15], antiulcer, and thrombosis [16].

Chalcone is a starting material for the synthesis of flavones and chalcones can be synthesized by many methods. In general, chalcones were prepared by Claisen-Schmidt condensation of electrophilic substituted benzaldehyde with substituted acetophenone as nucleophile in the presence of bases such as NaOH, KOH, $Ba(OH)_2$, LiOH, NaH, hydrotalcites, Zeolites, Na_2CO_3, K_2CO_3, magnesium t-butoxide, alumina, MgO, KF/natural phosphate, calcined $NaNO_3$-natural phosphates, and piperidine. Chalcones are also prepared by ultrasonic vibration and microwave irradiation techniques [17-19].

Green chemistry is the need of the day and hence it was planned to synthesize some chalcones in an eco-friendly way without using solvents. Thus, the synthesis involves the solvent-free solid state trituration methods involved Claisen-Schmidt reaction between acetophenone derivatives and substituted benzaldehydes in the presence of NaOH. The remaining chalcone was planned to synthesize by taking KOH as a base. Using these chalcone derivatives, it was contemplated to synthesis of some flavone derivatives from the corresponding chalcone by using dimethyl sulfoxide (DMSO)/I_2 [14].

METHODS

All the chemicals were obtained from commercial sources and used without further purification. Melting point was measured in digital melting point apparatus (Veego, VMP-DS) model. Infrared (IR) and mass spectra of synthesized compounds were taken by using IR spectrometer (NICOLET 6700, Thermo Scientific) and mass spectrometer (Advion Compact Mass Spectrometer) by ESI Techniques, respectively. ^{1}H nuclear magnetic resonance (NMR) spectral was recorded at room temperature on a 400 MHz liquid state NMR spectrometer in DMSO-d6 (Brüker Biospin, Switzerland) using tetramethylsilane as internal standard. The reactions were monitored by thin-layer chromatography (TLC) using precoated plates (Merck). All solvents used in thin layer chromatography were distilled before use.

General procedure for the synthesis of substituted chalcone (1A-1L, Scheme 1)

Method 1 (1A-1E)

About 24 mmol of aryl aldehyde (1.2 equivalent) were taken in mortal pestle triturated with NaOH powder added in portion wise with continuous trituration. 20 mmol 2-hydroxy acetophenone (1 equivalent) was added with continuous trituration. A solid yellow mass was formed with continuous trituration. The reaction was monitored by TLC. The formed yellow solid was immediately washed with hot methanol to get crude chalcone.

Method 2 (1F-1S)

2-Hydroxy acetophenone (1 equivalent) and benzaldehyde derivatives (1.2 equivalent) were dissolved in EtOH and KOH pallet (3 equivalent) was added. The reaction mixture was stirred at RT for 6-12 hrs until reaction completion was indicated by TLC. The reaction was worked up the mixture was poured onto crushed ice and acidified with dilute HCl (pH 5). The solid was recrystallized from dilute ethanol to get crystalline chalcone.

General procedure for the synthesis of all substituted flavones (2A-2L)

Synthesized 2-hydroxy arylchalcone (5 mmol) was taken in radial basis function, and 6 ml of DMSO was added in it. Then, catalytic amount

of I_2 was added to the reaction mixture and heat the content on oil bath at 110°C for 2-6 hrs. The reaction completion was indicated by TLC. The reaction was worked up the mixture was poured onto crushed ice and excess I_2 was removed by slow addition of sodium thiosulfate solution. The precipitated product was filtered by suction and solid was recrystallized from dilute ethanol to get crystalline flavone (Scheme 1).

RESULTS AND DISCUSSION

Synthesis of chalcone was achieved by claisen-schmidt condensation of 2-hydroxy acetophenone and various aromatic aldehyde derivatives by solvent free trituration (1A-1F) and conventional (1G-1L) method. From synthesized chalcone derivatives various flavone derivatives were synthesized. The synthesized chalcone was confirmed by various physicochemical means, TLC and IR spectrometer. The IR absorption spectrum band at 3600-3400 cm^{-1} indicated that the presence of hydroxyl groups and 1600-1660 cm^{-1} indicated the presence of α, β unsaturated carbonyl (>C=O) carbon in synthesized chalcone (Fig. 1 and Table 1).

Cyclization of chalcone into corresponding flavones was carried out using DMSO/I_2 as catalyst. The formation of flavones has been supported by TLC, physicochemical means and various spectral techniques (IR, mass and ^{1}H NMR). In flavones, the IR absorption spectrum band at 3020-3070 cm^{-1} indicated that the presence of aromatic(-C-H) stretching and 1600-1660 cm^{-1} indicated the presence of α, β unsaturated carbonyl (>C=O) carbon in synthesized flavones and absence of –OH group band confirmed the oxidation of chalcone into flavones.^{1}H NMR and mass spectral data also supported the formation of flavones derivatives as shown in spectral data section.

Spectral data of flavone derivatives

2-(2,3-dimethoxyphenyl)-4H-chromen-4-one (2A)

Molecular formula: $C_{17}H_{14}O_4$, yield: 78%, MP: 142-145°C, IR (KBr) cm^{-1}: 3062 (-CH aromatic str), 1653 (>C=O str), 1258, 1152 (R-O-Arstr), ^{1}H NMR (DMSO-d6), 400 MHz, δ (ppm): 3.92 (s, 6H, -OCH_3), 6.69 (s, 1H, pyrone ring), 7.60 (t, 2H, phenyl ring A), 7.35 (d, 2H, phenyl ring A), 8.02 (d, 1H, Ar-CH, ring B), 6.91 (d, 1H, Ar-CH, ring B), 7.19 (s, 1H, Ar-CH, ring B); Mass: 283.3 (M+1).

2-(3-hydroxyphenyl)-4H-chromen-4-one (2B)

Molecular formula: $C_{15}H_{10}O_3$, yield: 59%, MP: 139-142°C, IR (KBr) cm^{-1}: 3089 (-CH aromatic str), 3461 (-OH str), 1653 (>C=O str); ^{1}H NMR (DMSO-d6), 400 MHz, δ (ppm): 8.48 (s, 1H, -OH), 6.79 (s, 1H, pyrone ring), 7-7.90 (m, 4H, Ar-CH, ring A), 7.37-7.90 (m, 4H, Ar-CH, ring B); mass: 239.2 (M+1).

2-(4-methoxyphenyl)-4H-chromen-4-one (2C)

Molecular formula: $C_{16}H_{12}O_3$, yield: 75%, MP: 145-148°C, IR (KBr) cm^{-1}: 3059(-CH Aromatic str), 1628 (>C=O str), 1247, 1134 (R-O-Arstr); ^{1}H NMR (DMSO-d6), 400 MHz, δ (ppm): 3.83 (s, 3H, -OCH_3) 6.69 (s, 1H, pyrone ring), 7.34 (t, 1H, Ar-CH, ring A), 7.60 (t, 1H, Ar-CH, ring A), 8.17 (d, 1H, Ar-CH, ring A), 7.50 (d, 1H, Ar-CH, ring A), 6.95 (dd, 2H, Ar-CH, ring B), 7.81 (dd, 2H, Ar-CH, ring B); Mass: 253.3 (M+1).

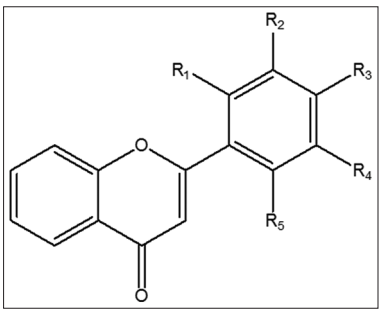
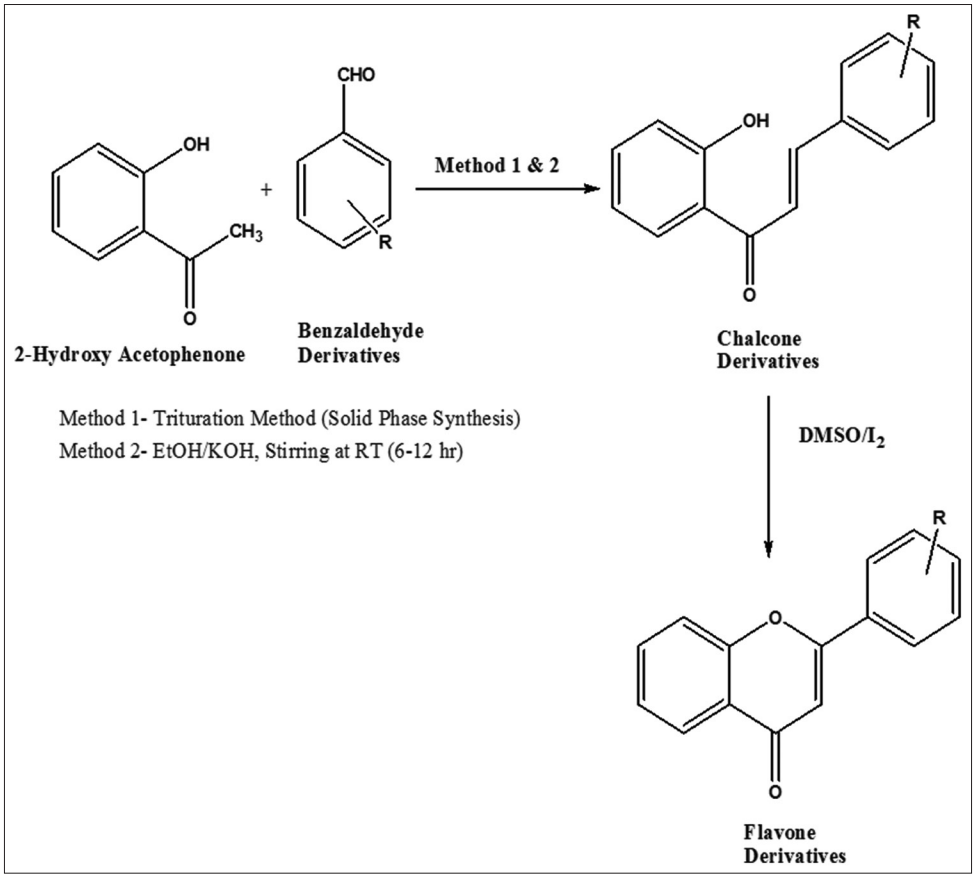


Fig. 1: General structure of chalcone



Scheme 1: Synthesis of chalcones by trituration (1A-1F) and conventional method (1G-1L) and flavone (2A-2L)

Table 1: Physicochemical and IR spectral data of chalcone derivatives

Compound ID	R_1	R_2	R_3	R_4	R_5	Melting point (°C)	Yield (%)	IR (cm^{-1})
1A	−H	$-OCH_3$	$-OCH_3$	−H	−H	92-94	86	3001 (Aromatic -C-H) str., 3600-3200 (O-H) str., 1695 (C=O) str., 1513, 1465 (C=C) str., 1266, 1152 (R-O-Ar) str.
1B	−H	−OH	−H	−H	−H	85-88	78	3030 (Aromatic -C-H) str., 3600-3200 (O-H) str., 1640 (C=O) str., 1488 (C=C) str.
1C	−H	−H	$-OCH_3$	−H	−H	78-80	83	3065 (Aromatic−C-H) str., 3600-3200 (O-H) str., 1637 (C=O) str., 1581, 1488 (C=C) str., 1261, 1152 (R-O-Ar) str.
1D	−H	−H	−Cl	−H	−H	82-84	68	3055 (Aromatic –C-H) str., 3600-3200 (O-H) str., 1635 (C=O) str., 1558, 1488 (C=C) str., 746 (Ar-Cl) str.
1E	−H	−H	−F	−H	−H	68-70	85	3055 (Aromatic –C-H) str., 3600-3200 (O-H) str., 1589 (C=O) str., 1513, 1494 (C=C) str.
1F	−H	−Cl	−H	−H	−H	80-83	75	3056 (Aromatic –C-H) str., 3600-3200 (O-H) str., 1647 (C=O) str., 1583, 1491 (C=C) str., 755 (Ar-Cl) str.
1G	−H	$-OCH_3$	−H	−H	−H	65-68	88	3010 (Aromatic –C-H) str., 3600-3200 (O-H) str., 1640 (C=O) str., 1576, 1486 (C=C) str., 1271, 1157 (R-O-Ar) str.
1H	$-OCH_3$	−H	$-OCH_3$	−H	$-OCH_3$	108-110	78	3035 (Aromatic –C-H) str., 3600-3200 (O-H) str., 1624 (C=O) str., 1576, 1488 (C=C) str., 1268 ,1156 (R-O-Ar) str.
1I	$-OCH_3$	$-OCH_3$	−H	−H	−H	115-117	86	3065 (Aromatic –C-H) str., 3600-3200 (O-H) str., 1640 (C=O) str., 1577, 1487 (C=C) str., 1272, 1159 (R-O-Ar) str.
1J	$-OCH_3$	−H	$-OCH_3$	−H	−H	106-108	75	3001 (Aromatic –C-H) str., 3600-3200 (O-H) str., 1636 (C=O) str., 1560, 1489 (C=C) str, 1282, 1158 (R-O-Ar) str.
1K	−H	−H	−H	−H	−H	78-80	86	3045 (Aromatic –C-H) str., 3600-3200 (O-H) str., 1640 (C=O) str., 1574, 1485 (C=C) str.,
1L	−H	−Br	−H	−H	−H	108-110	75	3058 (Aromatic –C-H) str., 3600-3200 (O-H) str., 1641 (C=O) str., 1575, 1485 (C=C) str.

IR: Infrared

2-(4-chlorophenyl)-4H-chromen-4-one (2D)

Molecular formula: $C_{15}H_9ClO_2$, yield: 65%, MP: 154-157°C, IR (KBr) cm^{-1}: 3066(-CH Aromatic str), 1621 (>C=O str), 771 (Ar-Clstr); ^{1}H NMR (DMSO-d6), 400 MHz, δ (ppm): 6.98 (s, 1H, pyrone ring), 7.13-8.31 (m, 4H, Ar-CH, ring A), 7.57 (dd, 2H, Ar-CH, ring B), 7.70 (dd, 2H, Ar-CH, ring B); mass: 257.2 (M+1).

2-(4-fluorophenyl)-4H-chromen-4-one (2E)

Molecular formula: $C_{15}H_9FO_2$, yield: 68%, MP: 152-154°C, IR (KBr) cm^{-1}: 3045 (-CH Aromatic str), 1601 (>C=O str); ^{1}H NMR (DMSO-d6), 400 MHz, δ (ppm): 6.73 (s, 1H, pyrone ring), 7.34 (t, 1H, Ar-CH, ring A), 7.67 (t, 1H, Ar-CH, ring A), 7.51 (d, 1H, Ar-CH, ring A), 8.17 (d, 1H, Ar-CH, ring A), 7.45 (dd, 2H, Ar-CH, ring B), 7.81 (dd, 2H, Ar-CH, ring B); mass: 241.2 (M+1).

2-(3-chlorophenyl)-4H-chromen-4-one (2F)

Molecular formula: $C_{15}H_9ClO_2$, yield: 85%, MP: 90-94°C, IR (KBr) cm^{-1}: 3030 (-CH Aromatic str), 1644 (>C=O str), 693 (Ar-Clstr); ^{1}H NMR (DMSO-d6), 400 MHz, δ (ppm): 7.16 (s, 1H, pyrone ring), 7.72 (t, 1H, Ar-CH, ring A), 7.67 (t, 1H, Ar-CH, ring A), 8.09 (d, 1H, Ar-CH, ring A), 8.12 (d, 1H, Ar-CH, ring A), 8.22 (s, 1H, Ar-CH, ring B), 7.90 (d, 1H, Ar-CH, ring B), 8.22 (s, 1H, Ar-CH, ring B), 7.98 (t, 1H, Ar-CH, ring B), 7.95 (d, 1H, Ar-CH, ring B); mass: 257.3 (M^+).

2-(3-methoxyphenyl)-4H-chromen-4-one (2G)

Molecular formula: $C_{16}H_{12}O_3$, yield: 79%, MP: 64-67°C, IR (KBr) cm^{-1}: 3045(-CH Aromatic str), 1629 (>C=O str), 1292, 1099 (R-O-Arstr); ^{1}H NMR (DMSO-d6), 400 MHz, δ (ppm): 3.95 (s, 3H, $-OCH_3$) 6.62 (s, 1H, pyrone ring), 7.84 (t, 1H, Ar-CH, ring A), 7.51 (t, 1H, Ar-CH, ring A), 7.69 (d, 1H, Ar-CH, ring A), 8.05 (d, 1H, Ar-CH, ring A), 6.26, 6.42 (m, 2H, Ar-CH, ring B), 7.31, 7.33 (m, 2H, Ar-CH, ring B); Mass: 252.2 (M^+).

2-(2,4,6-trimethoxyphenyl)-4H-chromen-4-one (2H)

Molecular formula: $C_{18}H_{16}O_5$, Yield: 66%, MP: 90-94°C, IR (KBr) cm^{-1}: 3030 (-CH Aromatic str), 1645 (>C=O str), 1279, 1157 (R-O-Arstr); ^{1}H NMR (DMSO-d6), 400 MHz, δ (ppm): 3.95 (s, 9H, $-OCH_3$) 6.62 (s, 1H, pyrone ring), 7.80(t, 1H, Ar-CH, ring A), 7.51 (t, 1H, Ar-CH, ring A), 7.69 (m, 1H, Ar-CH, ring A), 8.05 (m, 1H, Ar-CH, ring A), 6.26, 6.42 (m, 2H, Ar-CH, ring B), mass: 283.3 (M+1).

2-(2,3-dimethoxyphenyl)-4H-chromen-4-one (2I)

Molecular formula: $C_{17}H_{14}O_4$, Yield: 84%, MP: 102-105°C, IR (KBr) cm^{-1}: 3038 (-CH Aromatic str), 1641 (>C=O str), 1256, 1142 (R-O-Arstr); ^{1}H NMR (DMSO-d6), 400 MHz, δ (ppm): 3.00, 3.17 (s, 6H, $-OCH_3$) 6.78 (s, 1H, pyrone ring), 7.84 (t, 1H, Ar-CH, ring A), 7.52 (t, 1H, Ar-CH, ring A), 7.38 (d, 1H, Ar-CH, ring A), 8.08 (d, 1H, Ar-CH, ring A), 7.31, 7.27 (m, 2H, Ar-CH, ring B), 7.75 (d, 1H, Ar-CH, ring B) mass: 283.3 (M+1).

2-(2,4-dimethoxyphenyl)-4H-chromen-4-one (2J)

Molecular formula: $C_{17}H_{14}O_4$, yield: 76%, MP: 80-84°C, IR (KBr) cm^{-1}: 3056 (-CH Aromatic str), 1629 (>C=O str), 1280, 1152 (R-O-Arstr); ^{1}H NMR (DMSO-d6), 400 MHz, δ (ppm): 3.97 (s, 6H, $-OCH_3$) 6.93 (s, 1H, pyrone ring), 7.80 (t, 1H, Ar-CH, ring A), 7.48 (t, 1H, Ar-CH, ring A), 7.95 (d, 1H, Ar-CH, ring A), 8.04 (d, 1H, Ar-CH, ring A), 6.82 (s, 1H, Ar-CH, ring B), 6.76 (d, 1H, Ar-CH, ring B), 7.73 (d, 1H, Ar-CH, ring B), mass: 283.3 (M+1).

2-phenyl-4H-chromen-4-one (2K)

Molecular formula: $C_{15}H_{10}O_2$, yield: 59%, MP: 92-95°C, IR (KBr) cm^{-1}: 3045 (-CH Aromatic str), 1645 (>C=O str); ^{1}H NMR (DMSO-d6), 400 MHz, δ (ppm): 7.07 (s, 1H, pyrone ring), 7.82 (t, 1H, Ar-CH, ring A), 7.50 (t, 1H, Ar-CH, ring A), 8.12 (d, 1H, Ar-CH, ring A), 8.14 (d, 1H, Ar-CH, ring A),7.85 (d, 1H, Ar-CH, ring B), 8.06 (d, 1H, Ar-CH, ring B), 7.63, 7.61, 7.58 (m, 3H, Ar-CH, ring B), mass: 223.2 (M+1).

2-(3-bromophenyl)-4H-chromen-4-one (2L)

Molecular formula: $C_{15}H_9BrO_2$, yield: 68%, MP: 112-115°C, IR (KBr) cm^{-1}: 3058 (-CH Aromatic str), 1645 (>C=O str); ^1H NMR (DMSO-d6), 400 MHz, δ (ppm): 7.15 (s, 1H, pyrone ring), 7.57, 7.51 (m, 2H, Ar-CH, ring A), 7.50 (t, 1H, Ar-CH, ring A), 7.85 (d, 1H, Ar-CH, ring A), 7.86 (d, 1H, Ar-CH, ring A), 8.32 (s, 1H, Ar-CH, ring B), 8.15 (d, 1H, Ar-CH, ring B), 7.83 (t, 1H, Ar-CH, ring B), 8.05 (d, 1H, Ar-CH, ring B); mass: 301.2 (M^+).

CONCLUSION

The yield of chalcone derivatives (by green chemistry and conventional) were found to be in the range of 68-88% and by both the methods similar yield were obtained and the yield of flavone were lain between 58% and 85%.

The purity of compounds was ascertained by melting point and TLC. The synthesized compounds were further established by IR, ^1H NMR, and mass spectral studies. Based on spectral data, it was proved that all synthesized chalcone and flavone derivatives meet the standard values of various spectral techniques.

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