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Environmentally benign synthesis of substituted iodinated flavones as precursors for prenyl-/geranyl flavones from the corresponding chalcones

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RESEARCH ARTICLE

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ABSTRACT

Flavones have biological properties because of the existence of oxoheterocyclic ring moieties, and day by day create research interest areas because of their important biological activity. Iodine-substituted flavones were synthesized from the corresponding chalcones through an exhaustive iodination reaction. Generally, it is seen that halogenated flavones show better biological activity. Moreover, the introduction of iodine in the ring moiety facilitates the incorporation of highly active side chains, such as prenyl and geranyl groups through the formation of C-C bonds by numerous coupling reactions such as Sonogashira coupling. To achieve such target molecules, a planned chemical synthesis was conducted. For comparison, microwave irradiation (MWI) and conventional heating (CH) methods were used to synthesize a series of iodine-substituted flavone compounds with different substitutes (4a-d) from their corresponding chalcones (3a-d). Unfortunately, 3e chalcone (1-hydroxynapthalene substituted flavone) did not convert to 4e flavones. In the microwave method, a notable decrease in time required in the reaction and an increase in % yield of the reaction were remarked. Characterization and conformation of all synthesized compounds were done using ultraviolet, infrared, and nuclear magnetic resonance spectroscopy and elemental analysis.

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1. Introduction

Flavonoids are naturally obtained compounds that are widely distributed in the plant kingdom. Flavonols, flavones, flavanones, isoflavones, and chalcones are the classification of flavonoids according to the molecular structure [1,2]. Due to the various functions of flavones in plants and the different roles they play when they interact with other organisms, flavone compounds have inherent applications in the sectors of human health, pharmacology, and agriculture [3-5]. From the leguminosa or bean family, flavones are manufactured and used as a dietary complement. The flavonoid contains a coumarin nucleus that is a heteroaromatic part with different types of substituents that give excellent structural patterns for flavonoids. These types of phytochemicals, such as flavonoids, have extensive biological properties [6-8]. Prenylatedpolyphenols have a characteristic nature that shows biological activity, for example, antifungal, antioxidant, anticancer, and insecticidal properties. Furthermore, soyisoflavones and prenyl have the capability for harmonious and/or other chemoprevention therapies against long-term diseases such as menopause [9-12]. Due to their wide-range properties, flavones have attracted considerable attention in the area of cosmetics, food supplements, agrochemicals, and medicine in recent years [13,14]. Soy isoflavones such as genistein and daidzein, and their respective glycosidic conjugates of daidzein and genistein play a potential role in reducing the risk of lung, head and neck, prostate, and breast cancer for these compounds have received considerable attention from researchers [15,16]. Kato *et al.* published a report that both genistein, as well as daidzein, have anticancer effects against prostate cancer development at relatively early stages. Various studies suggested that genistein exerting antiproliferative effect depressed prostate cancer through the suppression of telomerase activity in prostate cancer cells. Telomerase activity is repressed by decreasing telomerase reverse transcriptase in human (hTERT) transcriptional activity and by post-translational modification of hTERT, which is carried out by genistein exerting antiproliferative effect [17,18].

Against Gram-positive and Gram-negative bacteria, various natural polyphenolics have shown considerable high activity that was reported in recent years. Therefore, it is suggested that the substitution of the coumarine ring might be an essential requirement for biological activity [19-21]. Such types of polyphenolics derivatives exhibit high activity for that the synthesis of suitable prenylflavones is a big challenge and

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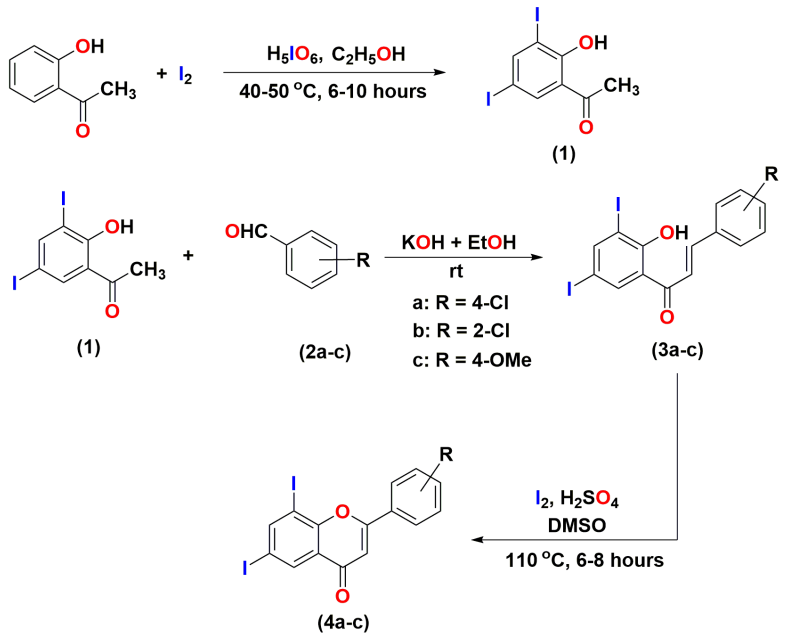


Scheme 1. Synthesis of compounds 1, 3a-c, 4a-c.

creates attention of the synthetic chemistry community. Therefore, some well-documented methods of synthesizing such a class of molecules were adopted using the microwave protocol in addition to the classical heating methodology. Consequently, a plethora of new compounds have been synthesized. Most importantly, this study aims to synthesize different substituted iodinated flavones with appreciable biological activity from iodinated chalcones and a comparative study between microwave irradiation (MWI) and conventional heating (CH) methods in synthesizing these flavones.

2. Experimental

2.1. Instrumentation

Fisher-John's electro-thermal melting point apparatus was used to determine the melting points. IR spectra were recorded by the NICOLET iS10 IR spectrophotometer on the KBr disc. A 400 MHz AVANCE Bruker NMR spectrometer was used to measure ^{1}H-NMR spectra using solvent $CDCl_3$ and TMS as internal standard at the Wazed Miah Science Research Center, Jahangirnagar University, Savar, Bangladesh. Parts per million (ppm) is used as units of chemical shift. The elemental analysis for carbon, hydrogen, and nitrogen was performed by the machine Elementar (Model no. Vario El Cube). The Shimadzu UV-1800 UV spectrophotometer was used to record ultraviolet spectra. The purity of the synthesized compounds was checked by TLC (silica gel-G). The TLC spots were visualized under an ultraviolet lamp and developed in an iodine chamber.

2.2. Synthesis

2.2.1. Synthesis of 1-(2-hydroxy-3, 5-diiodophenyl)ethan-1-one (1)

2.2.1.1. Microwave irradiation (MWI) method

In a two-necked round-bottom flask, (1.48 g, 10.88 mmol) 2-hydroxyacetophenone was dissolved in 8 mL of EtOH solvent, (2 g, 7.88 mmol) I_2 (iodine) and (0.82 g, 4.02 mmol in 7 mL of water) orthoperiodic acid were added one by one, respectively. The reaction mixture was irradiated for 8 min (5 sec × 32 times, 1 min interval/irradiation) under microwave irradiation (MWI). The mobile phase in TLC (EtOAc: *n*-hexane = 1:5) was used to monitor the reaction. The mixture was treated with cold distilled water to separate the solid products. Crude product was recrystallized using ethanol as a suitable solvent. A needle-shaped pale-yellow crystalline compound was obtained as a target compound [22,23].

2.2.1.2. Conventional heating (CH) method

In a two-necked round-bottom flask, (1.48 g, 10.88 mmol) 2-hydroxyacetophenone was dissolved in 12 mL of EtOH solvent, (2 g, 7.88 mmol) I_2 (Iodine) and (0.82 g, 4.02 mmol in 7 mL of water) orthoperiodic acid were added one by one, respectively. Subsequently, the reaction mixture was stirred for approximately 6 hours at 55 to 60 °C. The mobile phase in TLC (EtOAc: *n*-hexane = 1:5) was used to monitor the reaction. The mixture was treated with cold distilled water to separate the solid product. Crude product was recrystallized using ethanol as a suitable solvent. A needle-shaped, pale-yellow-colored, crystalline compound was obtained as a target compound (Schemes 1 and 2). The comparison of MWI and CH methods is given in Table 1.

1-(2-Hydroxy-3, 5-diiodophenyl)ethan-1-one (1): Color: Pale yellow crystalline solid. Yield: 77 % (MWI). M.p.: 120-121 °C. UV (EtOAc, λ_{max}, nm (log ε)): 365.5 (1.145). FT-IR (KBr, ν, cm^{-1}): 3441 (OH) (br, phenol), 3039 (C-H) (aromatic), 1569 (C=C) (aromatic), 1639 (C=O). ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 13.10 (s, 1H, ArOH), 8.23 (d, 1H, J_o = 2Hz, Ar-H), 8.02 (d, 1H, J_m = 2Hz, Ar-H), 2.67 (s, 3H, $COCH_3$). Anal. calc. for $C_8H_6I_2O_2$: C, 24.77; H, 1.56. Found: C, 24.98; H, 1.51%.

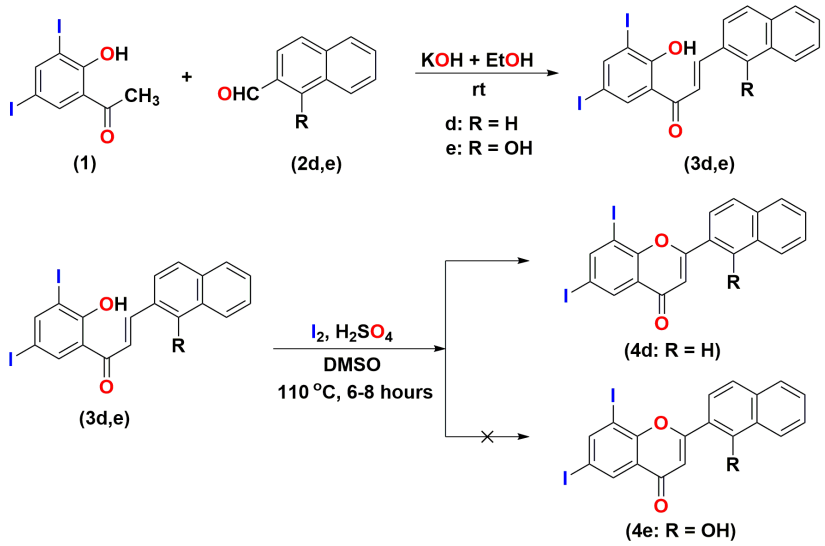
2.2.2. Synthesis of compound 3a-e from compound 1

2.2.2.1. Microwave Irradiation method

In a round bottom flask, an equal mole of 1-(2-hydroxy-3,5-diiodophenyl)ethan-1-one (1) (1.634 g, 3 mmol) and substituted benzaldehyde / napthaldehyde (*i.e.*, 4-chloro-benzaldehyde, 0.4215 g, 3 mmol) mixture was dissolved in 50-65 mL solution of alcoholic KOH (0.39 g, 7 mmol in EtOH).

Table 1. Comparison of MWI and CH methods for the prepared compounds.

Compound	Method	Reaction time	Solvent (mL)	Yield (%)
1	Microwave irradiation	8 min	8	77
	Conventional heating	6 hours	12	64
3a	Microwave irradiation	12 min	60	82
	Conventional heating	60 hours	180	71
3b	Microwave irradiation	15 min	60	77
	Conventional heating	80 hours	160	68
3c	Microwave irradiation	17 min	50	75
	Conventional heating	72 hours	170	67
3d	Microwave irradiation	18 min	65	78
	Conventional heating	60 hours	190	70
3e	Microwave irradiation	19 min	64	75
	Conventional heating	62 hours	192	64
4a	Microwave irradiation	10 min	12	74
	Conventional heating	6 hours	25	69
4b	Microwave irradiation	10 min	13	81
	Conventional heating	6 hours	27	72
4c	Microwave irradiation	10 min	13	75
	Conventional heating	6 hours	27	67
4d	Microwave irradiation	12 min	13	78
	Conventional heating	6 hours	27	69



Scheme 2. Synthesis of compounds 3d-e, 4d-e.

Subsequently, the reaction mixture was irradiated (10 sec × 72 times, 1 min interval/irradiation) for 12-19 minutes under MWI. The mobile phase in TLC (EtOAc: *n*-hexane = 1:5) was used to monitor the reaction. Then, 5% aq. HCl was added to neutralize the reaction mixture and finally ethyl acetate was used for extraction. Under reduced pressure, the solvent was removed and a semisolid mass of 2-hydroxy-chalcone was obtained. The purification of 2-hydroxychalcone was performed by recrystallization from ethanol.

2.2.2.2. Conventional heating method

In a round bottom flask, 0.83 mmol 1-(2-hydroxy-3,5-diiodophenyl)ethan-1-one (1) was dissolved in 20 mL of ethanol and in a beaker, 0.83 mmol of substituted benzaldehyde /napthaldehyde was dissolved in ethanol [23]. A 40% basic aqueous solution of KOH was prepared by 3.735 mmol (209 mg) of KOH. All three solutions were kept in an ice bath to cool them. After cooling, the round bottom flask was set on the magnetic stirrer (in an ice bath). Then the solution of substituted benzaldehyde/napthaldehyde was added to the solution of 1-(2-hydroxy-3,5-diiodophenyl)ethan-1-one (1) dropwise. In the next step, a 40% solution of KOH was added to the mixture dropwise. The final mixture was stirred at maximum 25 °C, maintaining the pH at 9 for 60-80 hours. The completion of the solution was monitored by TLC (thin layer chromatography) using a solvent system of ethyl acetate and *n*-hexane (1:5). After completion of the reaction, the mixture was neutralized with dilute HCl (5%) and the solid mass obtained was filtered off. The crude mass was purified by recrystallization from ethanol.

3-(4-Chlorophenyl)-1- (2-hydroxy-3, 5-diiodophenyl)prop-2-en-1-one (3a): Colour: Yellow solid. Yield: 82% (MWI). M.p.: 155-157 °C. UV (EtOAc, λ_{max}, nm, (log ε)): 336 (1.123). FT-IR (KBr, ν, cm^{-1}): 3404 (OH) (br, phenol), 2997 (C-H) (aromatic), 2933(C-H) (olefinic), 1691 (C=O) (ketone), 1635 (C=C), and 1570 (Ar-CC ring). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 13.70 (s, 1H, Ar-OH), 8.26 (d, 1H, *Jm* = 1.6 Hz, Ar-H), 8.16 (d, 1H, *Jm* = 1.6 Hz, Ar-H), 8.96 (d, 1H, *Jtrans* = 15.2 Hz, =C-H), 7.55 (d, 1H, *Jtrans* = 15.2 Hz, =C-H), 7.64 (d, 2H, *Jo* = 8.4 Hz, Ar-H), 7.46 (d, 2H, *Jo* = 8.4 Hz, Ar-H). Anal. calc. for $C_{15}H_9ClI_2O_2$: C, 35.29; H, 1.78. Found: C, 35.23; H, 1.74%.

3-(2-Chlorophenyl)-1-(2-hydroxy-3,5-diiodophenyl)prop-2-en-1-one (3b): Color: Yellowish solid. Yield: 77% (MWI). M.p.: 150-152 °C. UV (CH_3OH, λ_{max}, nm, (log ε)): 339 (0.477), 262 (0.385). FT-IR (KBr, ν, cm^{-1}): 3435 (OH) (br, phenol), 3061 (C-H) (aromatic); 1651 (C=O) (ketone), 1544 (C=C) (alkene), 1436 (C=C) (aromatic), 1245 (C-O), 1163 (C-C), 748 (C-Cl), 545(C-I). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 13.804 (s, 1H, Ar-OH), 8.39 (d, 1H, *Jtrans* = 15.6 Hz, =C-H), 8.27 (d, 1H, *Jm* = 1.6 Hz, Ar-H), 8.17 (d, 1H, *Jm* = 1.6 Hz, Ar-H), 7.84-7.82 (m, 1H, *Jo* = 7.6 Hz, *Jm* = 1.6 Hz, Ar-H), 7.55 (d, 1H, *Jtrans* = 15.6 Hz, =C-H), 7.52-7.50

(d, 1H, *Jo* = 8.8 Hz, *Jm* = 1.6 Hz, Ar-H), 7.45-7.43 (m, 1H, *Jo* = 7.2 Hz, *Jm*= 1.6 Hz, Ar-H), 7.41-7.37 (m, 1H, *Jo* = 7.6 Hz, *Jm* = 2 Hz, Ar-H). Anal. calcd. for $C_{15}H_9ClI_2O_2$: C, 35.29; H, 1.78. Found: C, 35.21; H, 1.76%.

1-(2-Hydroxy-3,5-diiodophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (3c): Color: Yellow crystalline solid. Yield: 75% (MWI). M.p.: 119-121 °C. UV (CH_3OH, λ_{max}, nm, (log ε)): 248 (0.445). FT-IR (KBr, ν, cm^{-1}): 3420 (OH) (br, phenol), 3049 (C-H) (aromatic), 1637 (C=O) (ketone), 1558 (C=C) (alkene), 1423 (C=C) (aromatic), 1174 (C-O), 1149 (C-C), 538 (C-I). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 13.12 (s, 1H, Ar-OH), 8.236 (d, 1H, *Jm* = 2 Hz, Ar-H), 8.18 (d, 1H, *Jm* = 2 Hz, Ar-H), 8.024 (d, 1H, *Jtrans* = 15 Hz, =C-H), 7.69 (d, 2H, *Jo* = 8.4 Hz, Ar-H), 7.44 (d, 1H, *Jtrans* = 15 Hz, =C-H), 6.99 (d, 2H, *Jo* = 8.4 Hz, Ar-H), 3.91 (s, 3H, Ar-O-CH_3). Anal. calcd. for $C_{16}H_{12}ClI_2O_3$: C, 37.97; H, 2.39. Found: C, 38.01; H, 2.37%.

1-(2-Hydroxy-3,5-diiodophenyl)-3-(naphthalen-2-yl)prop-2-en-1-one (3d): Color: Yellow crystalline solid. Yield: 78% (MWI). M.p.: 138-140 °C. UV (CH_3OH, λ_{max}, nm, (log ε)): 324 (0.533). FT-IR (KBr, ν, cm^{-1}): 3400 (OH) (br, phenol), 3047 (C-H) (aromatic), 1639 (C=O) (ketone), 1560 (C=C) (alkene), 1423 (C=C) (aromatic), 1240 (C-O), 1157 (C-C), 536 (C-I). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 13.85 (s, 1H, Ar-OH), 8.27 (d, 1H, *Jm* = 2 Hz, Ar-H), 8.25 (d, 1H, *Jm* = 2 Hz, Ar-H), 8.18 (d, 1H, *Jtrans* = 15.2 Hz, =C-H), 8.13 (s, 1H, Ar-H), 8.02 (d, 1H, *Jm* =1.6 Hz, *Jo* = 12 Hz, Ar-H), 7.95 (d, 1H, *Jo* = 9.2 Hz, Ar-H), 7.92-7.90 (m, 1H, Ar-H), 7.83 (m, 1H, *Jo* = 8.4 Hz, Ar-H), 7.70 (d, 1H, *Jtrans* = 15.2 Hz, =C-H), 7.61-7.55 (m, 2H, Ar-H). Anal. calcd. for $C_{19}H_{12}I_2O$: C, 43.38; H, 2.30. Found: C, 43.34; H, 2.24%.

1-(2-Hydroxy-3,5-diiodophenyl)-3-(1-hydroxynaphthalen-2-yl)prop-2-en-1-one (3e): Color: Yellow crystalline solid. Yield: 75% (MWI). M.p.: 135-137 °C. UV (CH_3OH, λ_{max}, nm, (log ε)): 339 (0.480). FT-IR (KBr, ν, cm^{-1}): 3331 (OH) (br, phenol), 3049 (C-H) (aromatic), 1645 (C=O) (ketone), 1573 (C=C) (alkene), 1421 (C=C) (aromatic), 1234 (C-O), 1166 (C-C), 536 (C-I). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 11.73 (s, 1H, Ar-OH), 8.27 (d, 1H, *Jo* = 8 Hz, Ar-H), 8.26 (d, 1H, *Jtrans* = 15.6 Hz, =C-H), 8.06 (d, 1H, *Jo* = 8.4 Hz, Ar-H), 7.91 (d, 1H, *Jo* = 8.8 Hz, Ar-H), 7.87-7.85 (m, 1H, Ar-H), 7.81 (m, 1H, *Jo* = 8.4 Hz, Ar-H), 7.77-7.73 (t, 1H, *Jtrans* = 15.6 Hz, =C-H), 7.60 (d, 1H, *Jo* = 8.4 Hz, Ar-H), 7.49-7.45 (m, 2H, Ar-H), 6.86 (s, 1H, Ar-OH, naphthalene). Anal. calc. for $C_{19}H_{12}I_2O_3$: C, 42.10; H, 2.23. Found: C, 42.08; H, 2.25%.

2.3. Synthesis of iodo-flavones (4a-e) from chalcones (3a-e)

Chalcone 3a (0.402 g, 1.37 mmol) was dissolved in solvent DMSO (12 mL) and conc. H_2SO_4 (2-3 drops) was added to maintain pH = 2-3. After stirring the solution, a small amount of crystalline iodine was carefully added [23,24]. The reaction mixture was then irradiated for 10 min under microwave (15 sec. irradiation/interval 30 sec). Using TLC, the reaction was monitored until the reaction was complete. The reaction mixture was cooled with distilled water and extracted with chloroform ($CHCl_3$). A 20% sodium thiosulphate aqueous solution was used to wash the organic layer and dried over anhydrous sodium sulphate. Crude diiodo-flavone 4a (Scheme 1) was recrystallized using ethylacetate as a solvent and a pure off-white crystalline solid was obtained.

The same compound 4a was also synthesized by the classical heating (CH) method and it took 6 hours at a temperature of 80 °C. All other iodo-flavones were also synthesized in a similar way (Schemes 1 and 2) at a temperature of 80-110 °C. However, we did not obtain the 4e compound (1-hydoxy-naphthalene substituted flavone) from 3e. The comparison of MWI and CH methods is given in Table 1.

2-(4-Chlorophenyl)-6, 8-diiodo-4H-chromen-4-one (4a): Color: Off white solid. Yield: 74% (MWI). M.p.: 206-208 °C. UV (CH_3OH, λ_{max}, nm, (log ε)): 271 (1.877). FT-IR (KBr, ν, cm^{-1}): 3057 (C-H) (aromatic), 2939 (C-H) (olefinic), 1645 (C=O) (ketone), 1600 (C=C), 1543 (Ar CC ring). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.51 (d, 1H, *Jm* = 2 Hz, Ar-H), 8.43 (d, 1H, *Jm* = 2 Hz, Ar-H), 7.98 (d, 2H, *Jo* = 8.4 Hz, Ar-H), 7.55 (d, 2H, *Jo* = 8.4 Hz, Ar-H), 6.84 (s, 1H, =C-H). Anal. calc. for $C_{15}H_7ClI_2O_2$: C, 35.46; H, 1.39. Found: C, 35.40; H, 1.35%.

2-(2-Chlorophenyl)-6, 8-diiodo-4H-chromen-4-one (4b): Color: Off-white solid. Yield: 81% (MWI). M.p.: 135-137 °C. UV (CH_3OH, λ_{max}, nm, (log ε)): 339 (0.477), 262 (0.385). FT-IR (KBr, ν, cm^{-1}): 3061 (C-H) (aromatic), 1651 (C=O) (ketone), 1544 (C=C) (alkene), 1436 (C=C) (aromatic), 1245 (C-O), 1163 (C-C), 748 (C-Cl), 545 (C-I). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.56 (s, 1H, Ar-H), 8.45 (s, 1H, Ar-H), 8.22 (d, 1H, *Jo* =15 Hz, Ar-H), 7.79 (d, 1H, *Jo* = 6.4 Hz, Ar-H), 7.59 (t, 1H, *Jo* = 7.6 Hz, Ar-H), 7.54-7.48 (m, 1H, Ar-H), 6.83 (s, 1H, =C-H). Anal. calc. for $C_{15}H_7ClI_2O_2$: C, 35.43; H, 1.39. Found: C, 35.39; H, 1.36%.

2-(4-Methoxyphenyl)-6, 8-diiodo-4H-chromen-4-one (4c): Colour: Off-white solid. Yield: 75% (MWI). M.p.: 162-165 °C. UV (CH_3OH, λ_{max}, nm, (log ε)): 323 (0.493), 258 (0.438). FT-IR (KBr, ν, cm^{-1}): 3062 (C-H) (aromatic), 1664 (C=O) (ketone), 1508 (C=C) (alkene), 1431 (C=C) (aromatic), 1226 (C-O), 1165 (C-C), 584 (C-I). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.55 (d, 1H, *Jo* = 2 Hz, Ar-H), 8.44 (d, 1H, *Jo* = 2 Hz, Ar-H), 8.04 (d, 2H, *Jo* = 9.2 Hz, Ar-H), 7.10 (d, 2H, *Jo* = 9.2 Hz, Ar-H), 6.94 (s, 1H, =C-H), 3.94 (3H, s, Ar-O-CH_3). Anal. calc. for $C_{16}H_{10}I_2O_3$: C, 38.11; H, 2.01. Found: C, 38.08; H, 2.00%.

2-(Naphthalen-2-yl)-6, 8-diiodo-4H-chromen-4-one (4d): Colour: Off-white fluffy crystalline solid. Yield: 78% (MWI). M.p.: 175-177 °C. UV (CH_3OH, λ_{max}, nm, (log ε)): 237 (0.367), 331 (0.159). FT-IR (KBr, ν, cm^{-1}): 3049 (C-H) (aromatic), 1647 (C=O) (ketone), 1579 (C=C) (alkene), 1431 (C=C) (aromatic), 1226 (C-O), 1163 (C-C), 543 (C-I). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.26 (d, 1H, *Jm* = 2 Hz, Ar-H), 8.21 (d, 1H, *Jm* = 2 Hz, Ar-H), 8.13 (d, 1H, *Jo* = 7.2 Hz Ar-H), 8.11 (d, 1H, *Jm* = 1.6 Hz, Ar-H), 8.03 (m, 1H, *Jo* = 8.4 Hz Ar-H), 7.97 (m, 1H, *Jo* = 8 Hz, Ar-H), 7.93 (m, 1H, *Jo* = 7.2 Hz, Ar-H), 7.63 (m, 2H, *Jo* = 8 Hz, *Jo* = 7.2 Hz Ar-H), 7.05 (s, 1H, =C-H). Anal. calc. for $C_{19}H_{10}I_2O_2$: C, 43.54; H, 1.92. Found: C, 43.50; H, 1.88%.

3. Results and discussion

2-Hydroxyacetophenone is an interesting synthetic precursor in most organic reactions. Many heterocyclic compounds can be synthesized using 2-hydroxyacetophenone [25,26]. However, in the field of flavonoid chemistry, it is essential to introduce prenyl/geranyl side chains into the aromatic moiety to achieve target molecules of high potency in biological or food supplements [27]. In EtOH, 2-hydroxyacetophenone, I_2, and ortho-periodic acid were dissolved. The mixture was irradiated under MW conditions to yield diiodo compound 1 with fairly good yield. The characterization of compound 1 was done using some notable physical techniques such as proton NMR. The phenolic OH proton appeared at δ 13.10 ppm as a singlet. Other peaks appeared at δ 8.23 and 8.02 ppm for two aromatic protons in the meta position having the coupling constant value J_m = 1.6 Hz. MW-assisted condensation of compound 1 with 4-chlorobenzaldehyde (2a) in a minimal amount of alcoholic KOH solution gave 3-(4-chlorophenyl)-1-(2-hydroxy-3, 5-diiodophenyl) prop-2-en-1-one (3a) (Scheme 1). Chalcone 3a structure was determined using ^{1}H NMR spectral data. Two olefinic protons ^{1}H NMR peaks at δ 8.96 and 7.55 ppm and a coupling *J* value of 15.2 Hz were confirmed to the *trans*-coupling interaction. In addition, the prominent peaks are at 13.70 for the phenolic OH proton. Two aromatic protons of the iodo-ring appeared at δ 8.26 and 8.16 ppm as doublets showing 1.6 Hz as a metacoupling constant. Other protons showed their peaks as expected. Other chalcones (3b-e) were obtained almost in a similar way in high yields, and their spectral data were found to be justified by their structural features. The next step was as crucial as it afforded the target molecules. Consequently, compound **3a** by the ring closure reaction provided the desired flavone 4a in 74% yield. The reaction was carried out in the

presence of the minimum amount of dimethyl sulfoxide (DMSO) as a solvent, iodine, and sulfuric acid (catalytic amount) under microwave irradiation. The evidential confirmation of the formation of flavone 4a by identifying a characteristic peak for flavone appeared at δ 6.84 ppm singlet peak for the =C-H. For the substituted phenyl (B) ring aromatic protons at δ 7.98 and 7.55 ppm a doublet pattern appeared. The splitting of the para-substituted aromatic protons showed that the coupling was found to be 8.4 Hz. Furthermore, the microanalysis results of the compound are consistent with the calculated value. Similarly, all other compounds 4b-d were synthesized in high yields which are described in the experimental section (Schemes 1 and 2). In AcOH and H_2SO_4 mixtures using the conventional heating method, the same ring closure reaction was also achieved. However, with the conventional method, lower yields were obtained compared to those obtained with the microwave method. Conventional heating cyclization of 2-hydroxychalcone is very useful in the presence of a catalytic amount of iodine in DMSO, but a large volume of DMSO is required for successful reaction. Periodic acid-mediated iodination of hydroxyacetophenone was easier. There are some advantages of the method, such as aryl iodide (65-90%), fair to good yield, and short reaction time (10-12 min). On the basis of spectral and elemental data, the aryl iodide structure was established. The reaction of chalcone with iodine occurred smoothly because the mode of reaction was easy. It is predicted that the reaction follows a nucleophilic path with iodine. The microwave irradiation process in the presence of iodine reagents provides a faster reaction pathway, and it also has potential from environmental and economic standpoints. Here, H_2SO_4 was used as a catalyst that opens a catalytic pathway to convert into a target product by comprising enhancement of the attack by the ring A, OH group on the beta (β) carbon to produce an intermediate. However, it was observed that the cyclization of chalcone 3e was unsuccessful. This is probably due to the proximity of the 2-OH group which prevented cyclization for the steric hindered position.

4. Conclusions

Flavonoids are heterocyclic moiety-containing molecules that are essential in the field of food supplements and for the preparation of other bioactive compounds. Efficient methods to access these heterocycles have been very crucial recently in the field of synthesis. We report here the formation of these heterocycles and the introduction of iodine in the aromatic moiety, which practically facilitated the production of more desirable bioactive side chains such as prenyl or geranyl groups. Consequently, molecular iodine with periodic acid is being used for the synthesis of iodoflavones from their precursor 2-hydroxy chalcones. This is an exhaustive iodination for the possible way to achieve further prenylation or allylation by using Claisen-Schmidt condensation. A series of chalcones (3a-e) were synthesized for better and simple polyphenolics and related compounds. The cyclization of chalcones gave the corresponding flavones (4a-d). The results are obtained by using a minimal amount of DMSO, iodine, and a few drops of sulfuric acid. Flavones were obtained as target molecules in better yields under the microwave reaction protocol. These molecules were also synthesized under conventional heating methods. Undoubtedly, the MW procedure was much better regarding product yield, reaction time, and of course the amount of solvent.

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CRediT authorship contribution statement

Conceptualization: Mohammad Mamun Hossain, Sumaiya Khan; Methodology: Sumaiya Khan, Mohammad Mamun Hossain; Validation: Sumaiya Khan, Umme Aiman Liza, Mohammad Mamun Hossain; Synthesis: Dipan Banik, Md Aman Ullah Aman, Amit Chandra Arjaya; Formal Analysis:, Sumaiya Khan, Umme Aiman Liza, Dipan Banik, Md Aman Ullah Aman, Amit Chandra Arjaya, Kamrunnahar Happy, Mohammad Mamun Hossain; Investigation: Sumaiya Khan, Dipan Banik, Mohammad Mamun Hossain; Resources: Mohammad Mamun Hossain, Sumaiya Khan, Umme Aiman Liza; Data Correction: Sumaiya Khan, Umme Aiman Liza, Dipan Banik, Md Aman Ullah Aman, Kamrunnahar Happy, Amit Chandra Arjaya, Mohammad Mamun Hossain; Writing - Original Draft: Mohammad Mamun Hossain, Sumaiya Khan, Umme Aiman Liza; Writing - Review and Editing: Mohammad Mamun Hossain, Sumaiya Khan, Umme Aiman Liza; Visualization: Mohammad Mamun Hossain, Sumaiya Khan, Umme Aiman Liza; Funding acquisition: Mohammad Mamun Hossain, Sumaiya Khan, Umme Aiman Liza; Supervision: Mohammad Mamun Hossain, Sumaiya Khan; Project Administration: Mohammad Mamun Hossain, Sumaiya Khan.

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