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Ultrasound Promoted Stereoselective Synthesis of 2,3-Dihydrobenzofuran Appended Chalcones at Ambient Temperature

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ABSTRACT

In the present investigation, an ultrasound promoted the synthesis of a series of (*E*)-3-(2,3-dihydrobenzofuran 5-yl)-1-(aryl)prop-2-en-1-one derivatives from 2,3-dihydrobenzofuran-5-carbaldehyde and various aromatic ketones under clean conditions. The application of ultrasound irradiation in organic reactions is one of the incredible tools of green chemistry as reactions can be carried out rapidly under neat conditions. A library of a novel (*E*)-3-(2,3-dihydrobenzofuran-5-yl)-1-(aryl)prop-2-en-1-one chalcone derivatives were synthesized in good to excellent yield under ultrasonic irradiation. The structures of all synthesized chalcone derivatives synthesized in this study have been established by using FT-IR, ^{1}H NMR, ^{13}C NMR, and HRMS techniques. The stereochemistry around C=C in the chalcones was shown to be *trans* by ^{1}H NMR (J_{ab} = 15.5Hz). The benefits of the present synthesis include mild reaction conditions, high yield, purification by non-chromatographic strategy and short reaction times, demonstrating the significance of this protocol in terms of waste reduction and energy efficiency.

KEYWORDS

2,3-Dihydrobenzofuran-5-carbaldehyde, ultrasound irradiation, green chemistry, *trans* chalcone.

1. Introduction

2,3-dihydrobenzofuran-5-carbaldehyde is a fused organic molecule wherein benzene is fused with a dihydrofuran ring. It has been used for the synthesis of a privileged scaffold 1,2,6,7-tetrahydro-8*H*-indeno[5,4-*b*]furan-8-one (used for the synthesis of ramelteon). The dihydrofuran ring has been identified as a necessary pharmacophore by which ramelteon works as a sleep agent in people having sleep-onset insomnia.[1,2] Noteworthy examples of synthetic intermediates and drugs containing dihydrobenzofuran (Fig. 1) are 1,2,6,7-tetrahydro-8*H*-indeno[5,4-*b*]furan-8-one (**1**), ramelteon (**2**), tasimelteon (**3**), 1-(2,3-dihydrobenzofuran-5-yl)propan-2-amine (**4**), 1-(2,3-dihydrobenzofuran-5-yl)-N-methylpropan-2-amine (**5**) and ((1*R*,2*R*)-2-(2,3-dihydrobenzofuran-4-yl)cyclopropyl) methanol (**6**). The presence of the dihydrofuran ring in 2,3-dihydrobenzofuran-5-carbaldehyde attracted us to synthesize a new series of chalcones with potential medicinal properties.

Chalcone is a common and simple scaffold found in many naturally occurring compounds showing excellent biological activities.[3] Chalcones are a notable class of compounds, they also act as vital intermediates for the development of a variety of biologically potent heterocyclic compounds.[4–6] Chalcones display a wide scope of biological properties, most likely because of their small structures and Michael acceptor features, which make them tolerant to various biomolecules and enabling them to react or interact with them. The Michael acceptor site can be tuned to augment the biological potential of chalcones.[7] Chalcones containing a heterocyclic moiety display excellent biological profiles, including antiproliferative and anticancer,[8–13] antioxidant,[14,15] antiviral,[16–19] anti-tubercular,[20–22] antimicrobial,[23–26] anti-Alzheimer,[27] and antihypertensive properties.[28] Some naturally isolated chalcones are explored as potent anticancer, anti-HIV, antioxidant, antimicrobial and anti-inflammatory agents.[29–34] The structural modification of aryl rings, supplanting of aryl rings and molecular hybridization through conjugation with pharmacologically active platforms for the improvement of anticancer properties have empowered advancement of new chalcones with potential therapeutic adequacy in diverse pharmacological applications. On these grounds, chalcones are considered important structures in medicinal chemistry.

The literature shows that different strategies have been used for the synthesis of chalcones.[35] A large portion of reported strategies either require harsh conditions or prolonged reaction times.[36] Organic syntheses utilizing the principles of green chemistry is the need of the present as well as the future. Numerous green chemistry oriented organic synthesis methods have been developed in order to synthesize a wide range of compounds with less environmental hazards.[37–39] A standout amongst the most productive strategies as far as reaction time and yield, is ultrasound irradiation.[40] Organic synthesis based on ultrasound irradiation has attracted the attention of chemists in the last two decades. In this regard, sonochemistry has been rapidly advanced in recent years and it is considered to be an important tool for green chemistry in terms of waste minimization and energy conservation. Ultrasound can adjust the selectivity performance of the reaction and enhances the rate of reaction; hence it has been employed more frequently for organic transformations. Under ultrasound irradiation, the reaction time diminishes considerably, the yields are higher, and the reaction conditions are benign. In continuation of our interest in the development of mild, operationally simple and environment-friendly protocols for the synthesis of pharmacologically important compounds, we envisaged access to the new

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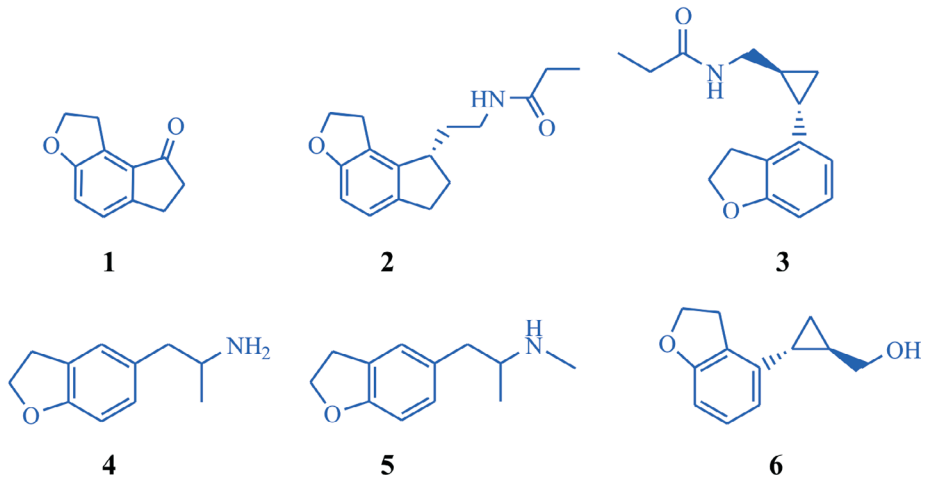


Figure 1 Some biologically important intermediates and medicinal agents are containing a dihydrobenzofuran ring.

series of (*E*)-3-(2,3-dihydrobenzofuran-5-yl)-1-(aryl)prop-2-en-1-one derivatives (**9a-9n**) of biological importance. Herein, we report the rapid and facile synthesis of (*E*)-3-(2,3-dihydrobenzofuran-5-yl)-1-(aryl)prop-2-en-1-one derivatives by using 2,3-dihydrobenzofuran-5-carbaldehyde and various aromatic ketones under ultrasonic irradiation. To the best of our knowledge, this is the first report on the synthesis of (*E*)-3-(2,3-dihydrobenzofuran-5-yl)-1-(aryl)prop-2-en-1-one derivatives under ultrasonic irradiation. The utility and applicability of this green protocol are enhanced by its simple work-up procedure, rendering it readily adaptable for use in automated synthesis. The overall reaction is depicted in Scheme 1.

2. Experimental

2.1. General Remarks

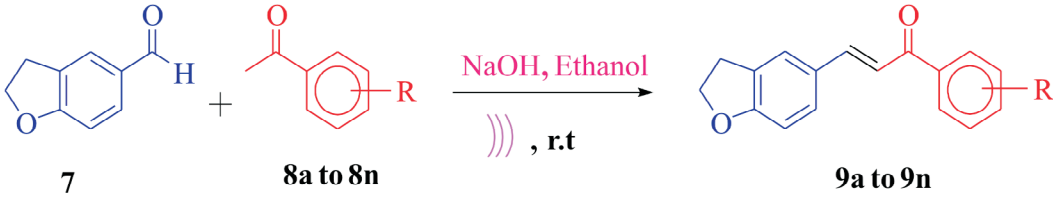
2,3-Dihydrobenzofuran-5-carbaldehyde was purchased from MS Life Sciences, Hyderabad, India. Other chemicals (Make: Sigma-Aldrich, Merck, and Avra synthesis) with high purity were purchased from local distributors. All the chemicals were used as received without any further purification. Melting points were determined in open capillaries and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance III HD NMR 500 MHz using $CDCl_3$ as a solvent, FT-IR spectra were obtained with potassium bromide pellets and HRMS were recorded on a Bruker Impact HRMS with ESI as a source. All reactions reported in this study were monitored using thin-layer chromatography using aluminium sheets coated with silica gel 60 F254 (Merck).

2.2. General Procedure for the Synthesis of (*E*)-3-(2,3-dihydrobenzofuran-5-yl)-1-(aryl)prop-2-en-1-one Derivatives

2,3-Dihydrobenzofuran-5-carbaldehyde (1 mmol), substituted acetophenones (1 mmol), absolute ethanol (5 mL), and 40 % sodium hydroxide (20 mmol diluted up to 2 mL) were added in a Pyrex flask (25 mL). The alkaline mixture was then exposed to ultrasound irradiation at room temperature for the period as indicated in Table 5. The reaction was monitored by thin-layer chromatography (eluent 20:80: ethyl acetate: hexane). The reaction mixture was quenched by pouring on ice. After this, the resulting mixture was acidified by using dilute HCl and the resulting precipitate was then filtered and dried to give the desired product. The obtained product was recrystallized from hot ethanol. The synthesized pure products were characterized by FT-IR, ^{1}HNMR, ^{13}C NMR and HRMS analytical methods.

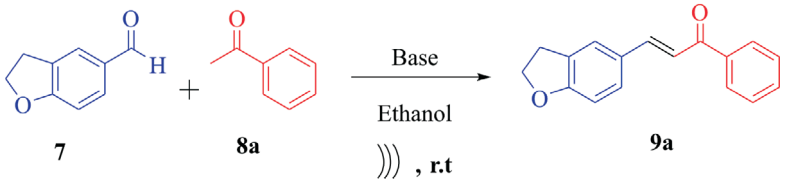
3. Results and Discussion

A broad range of chalcone analogs can conveniently be prepared from existing readily available substituted acetophenones and 2,3-dihydrobenzofuran-5-carbaldehyde. The synthesis of chalcones was accomplished by means of the Claisen-Schmidt reaction between 2,3-dihydrobenzofuran-5-carbaldehyde and various aromatic ketones. This scheme was envisaged to be highly advantageous due to the easy availability of a diverse range of aromatic ketones. The Claisen-Schmidt condensation between 2,3-dihydrobenzofuran-5-carbaldehyde (**7**) and acetophenone (**8a**) was selected as a model reaction for the optimization of reaction conditions for the synthesis of chalcones. The choice of base for the Claisen-Schmidt reaction is important to the success of this protocol. In order to explore the effect of different bases on the model reaction, the investigation was initiated with the selection of various bases. The easily available and common bases such as NaOH, KOH, K_2CO_3, Na_2CO_3, $NaHCO_3$, NaOMe, piperidine, pyrrolidine, $Li(OH).H_2O$, NEt_3 and pyridine were screened for a model reaction (Table 1). The results obtained for a large portion of bases indicate the yield of the product **9a** was not very satisfactory and they require a longer time for the completion of a reaction. It was revealed that the NaOH is a better choice as it furnished a maximum yield of **9a** within shorter reaction time. To check the precise amount of NaOH, we varied the amount of NaOH from 5 mmol to 50 mmol (Table 2). When the amount NaOH was increased from 5 mmol to 20 mmol, the yield of **9a** was found to increase with an overall reduction in completion time. However, the yield of **9a** dimin-



Scheme 1
Synthesis of (E)-3-(2,3-dihydrobenzofuran-5-yl)-1-(aryl)prop-2-en-1-one derivatives under ultrasonic irradiation.

Table 1 Effect of various bases on the synthesis of (*E*)-3-(2,3-dihydrobenzofuran-5-yl)-1-phenylprop-2-en-1-one (**9a**).[a]



7 **8a** **9a**

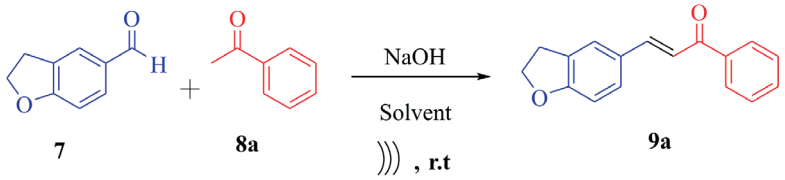
Entry	Base[b]	Time/min	Yield[c]/%
1	K_2CO_3	250	56
2	Na_2CO_3	270	54
3	$NaHCO_3$	280	45
4	NaOMe	170	58
5	Piperidine	130	64
6	Pyrroludine	120	65
7	$Li(OH).H_2O$	110	60
8	NEt_3	290	48
9	KOH	45	85
10	Pyridine	350	35
11	NaOH	50	95

[a] Reaction conditions: 2,3-dihydrobenzofuran-5-carbaldehyde (1 mmol), acetophenone (1 mmol), base (20 mmol), ethanol (5 mL).
[b] Diluted in water up to 2 mL.
[c] Isolated yield of pure product.

ished when the amount of NaOH was increased from 20 mmol to 50 mmol. We found that 20 mmol of sodium hydroxide was sufficient to ensure the reaction proceeded successfully. At the beginning of the selection of the best solvent, we applied the model reaction under solvent-free conditions and in the presence of various solvents (Table 3). The solvent-free reaction furnished the desired chalcone (**9a**) in very poor yield (**entry 1**). By contrast, the model reaction in other solvents afforded the desired chalcone in a satisfactory amount. A polar protic solvent such as ethanol and methanol were observed to be the most adequate as they yielded the chalcone in excellent yield. The formation of desired chalcone in the presence of polar aprotic solvents (CH_3CN, DMF, DMSO, THF) was more worthwhile in comparison to less polar and non-polar solvents (CH_2Cl_2 $CHCl_3$, $PhCH_3$, CCl_4), yet not as efficient as in the presence of ethanol and methanol. The hydrogen bond-forming ability of ethanol and methanol makes them superior over other solvents. Among all the employed solvents, ethanol was found to be the most efficient in terms of reaction time and yield and was utilized for further investigations.

After this, traditional methods which are often used to achieve the desired goal were considered. Two traditional stirring and reflux methods were employed to compare with the expeditious ultrasound technique. The data obtained using these conventional methods suggest that ultrasonication is very much better in terms of yield and time (Table 4). These reactions require

Table 2 Optimization of a base for the synthesis of **9a**.[a]

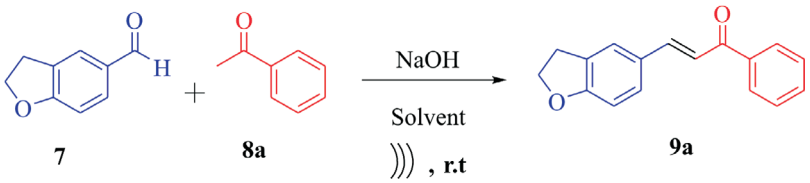


7 **8a** **9a**

Entry	NaOH[b]/mmol	Time /min	Solvent	Yield[c]/%
1	5	320	Ethanol	20
2	10	240	Ethanol	50
3	15	100	Ethanol	58
4	20	50	Ethanol	95
5	25	45	Ethanol	94
6	30	42	Ethanol	90
7	35	40	Ethanol	88
8	40	40	Ethanol	87
9	45	38	Ethanol	80
10	50	35	Ethanol	78

[a] Reaction conditions: 2,3-dihydrobenzofuran-5-carbaldehyde (1 mmol), acetophenone (1 mmol), ethanol (5 mL).
[b] Diluted in water up to 2 mL (except for 50 mmol).
[c] Isolated yield of pure product.

Table 3 Comparative analysis of various solvents for the synthesis of **9a**.[a]

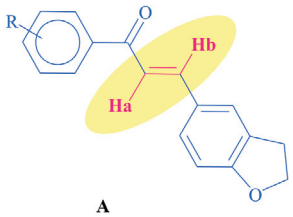


7 8a 9a

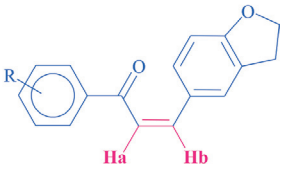
Entry	Solvent	Time/min	Yield/%
1	Solvent-free	200	20
2	Acetonitrile	120	58
3	CCl_4	150	51
4	Ethylene dichloride	160	49
5	THF	130	63
6	Methanol	60	80
7	DMSO	150	45
8	DMF	160	40
9	Dichloromethane	145	48
10	Ethanol	50	95

[a] Reaction conditions: 2,3-dihydrobenzofuran-5-carbaldehyde (1 mmol), acetophenone (1 mmol), NaOH (20 mmol diluted up to 2 mL), solvent (5 mL).
[b] Isolated yield of pure product.

longer reaction times with lower yields, as compared to similar reactions under ultrasound irradiation. Following the establishment of optimal conditions to evaluate the scope and limitations of this green strategy, the present protocol was extended to a broader range of aromatic ketones and heterocyclic ketones. Results of the obtained yields tabulated in Table 5 indicate that an array of functionality was tolerated under optimized reaction conditions. Results showed that, in general, the reactions were clean and the isolated compounds were obtained, after crystallization without further purification by tedious column chromatography. It was interesting to note that the nature of functional groups on an aromatic ring in aromatic ketones has no distinct effect on the reaction time and yield as aromatic ketones possessing electron releasing as well as electron attracting groups furnished corresponding chalcones in equally good yields. Besides, heterocyclic ketones such as 3-acetyl pyridine and 2-acetyl thiophene also afforded good yield of the corresponding chalcone. The physical properties were determined and structures were confirmed by FT-IR, NMR, and HRMS spectra. The characteristic pattern of *trans*-coupling constant (J = >15 Hz) was observed in the ^{1}H NMR spectra of all compounds synthesized, suggesting *cis* isomers were not obtained. Inspection of ^{1}H NMR spectral data indicated that the compounds were geometrically pure and suggested that the C=C in the enone linkage is in the *trans*-conformation.



A

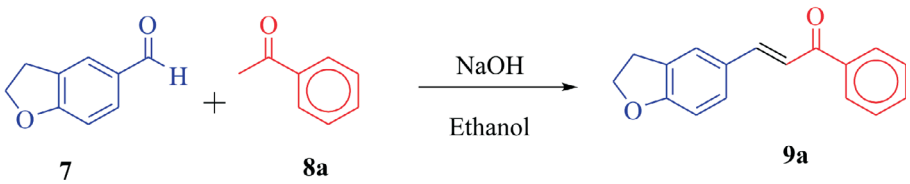


B

Not obtained

The probable reaction mechanism[41] for the synthesis of chalcones is outlined in Scheme 2. Initially, the carbanion is generated by base induced deprotonation of acetophenone to give enolate anion (**I**) followed by nucleophilic attack on the carbonyl carbon of 2,3-dihydrobenzofuran-5-carbaldehyde affording β-hydroxy ketone (**II**) which on elimination eliminates water molecule prompting the formation of desired chalcone (**III**).

Table 4 Comparison between ultrasonic, stirring and reflux methods for the synthesis of **9a**.[a]

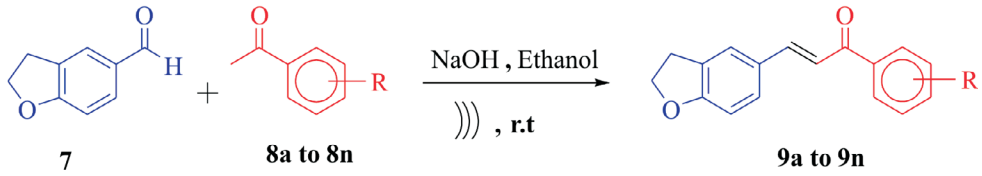


7 8a 9a

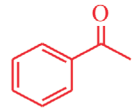
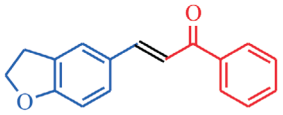
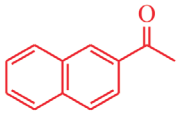
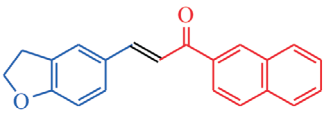
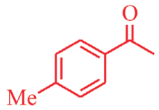
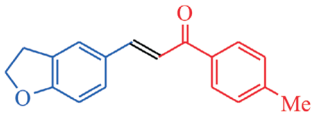
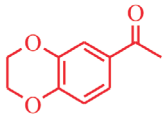
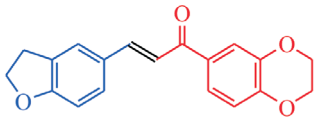
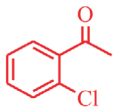
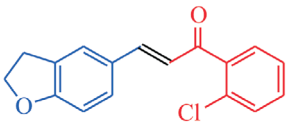
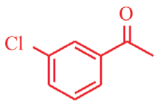
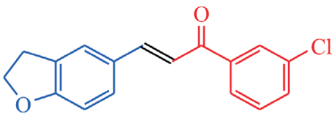
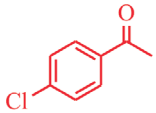
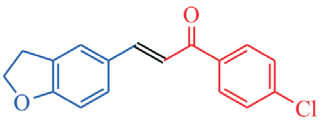
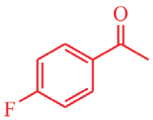
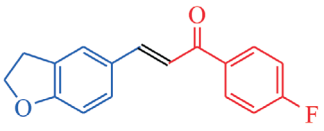
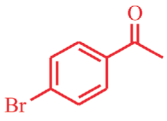
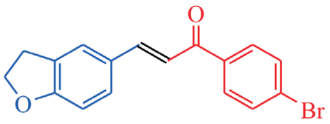
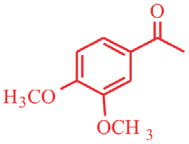
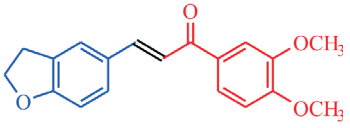
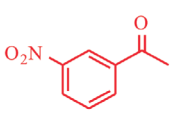
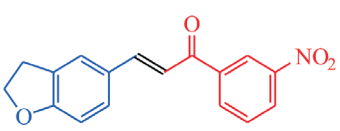
Entry	Method	Time/min	Yield[b]/%
1	Reflux at 60 °C	120	45
2	Stirring at rt	720	88
3	Ultrasound irradiation	50	95

[a] Reaction conditions:2,3-dihydrobenzofuran-5-carbaldehyde (1 mmol), acetophenone (1 mmol), NaOH (20 mmol diluted up to 2 mL).
[b] Isolated yield of pure product.

Table 5 Synthesis of (*E*)-3-(2,3-dihydrobenzofuran-5-yl)-1-(aryl)prop-2-en-1-one derivatives.[a]

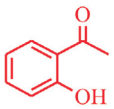
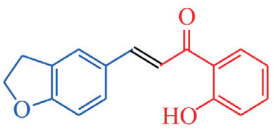
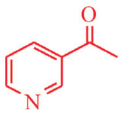
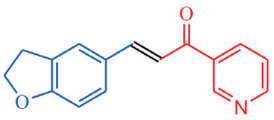
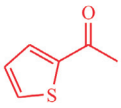
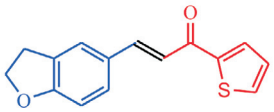


7 **8a to 8n** **9a to 9n**

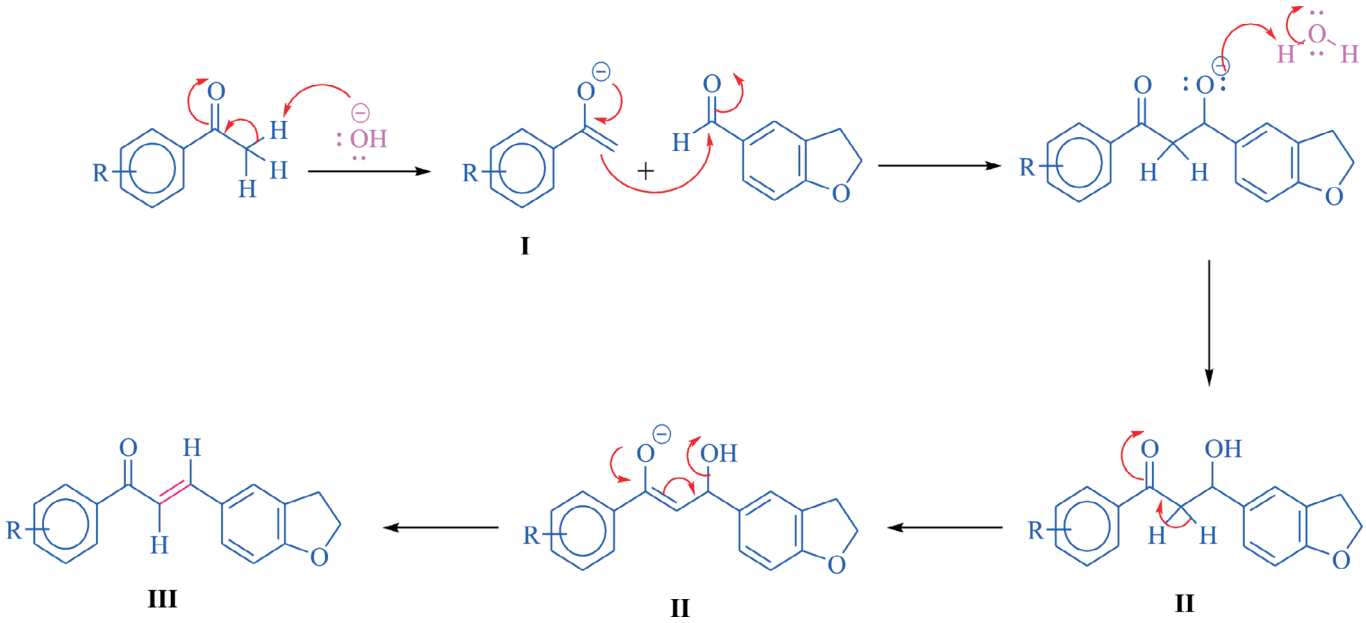
Entry	Ketone	Chalcone	Time/min	Yield[b]/%	M.P./°C
9a			50	95	108
9b			45	93	140
9c			48	89	135
9d			28	96	179
9e			22	88	105
9f			25	95	115
9g			30	97	169
9h			40	80	155
9i			45	85	159
9j			50	86	156
9k			20	90	157

Continued on p. 40

Table 5 (Continued).

Entry	Ketone	Chalcone	Time/min	Yield [b]/%	M.P./°C
9l			45	81	118
9m			35	91	140
3n			38	90	105

[a] Reaction conditions: 2,3-dihydrobenzofuran-5-carbaldehyde (1 mmol), substituted acetophenone (1 mmol), NaOH (20 mmol diluted up to 2 mL), ethanol (5 mL).
[b] Isolated yield of pure product.



Scheme 2
Proposed reaction mechanism.

4. Spectral Data of Synthesized Compounds

9a – (*E*)-3-(2,3-dihydrobenzofuran-5-yl)-1-phenylprop-2-en-1-one: pale yellow solid; m.p. 108 °C; FT-IR ν_{max} (KBr; cm^{-1}): 2914.44, 2850.79, 1651.07, 1568.13, 1489.05, 1436.97, 1327.03, 1240.23, 1209.37, 1097.50, 1004.91; δ_H (500 MHz; Choloroform-d): 8.06–7.97 (m, 2H), 7.78 (d, *J* = 15.6 Hz, 1H), 7.62–7.35 (m, 6H), 6.82 (d, *J* = 8.2 Hz, 1H), 4.65 (t, *J* = 8.7 Hz, 2H), 3.26 (t, *J* = 8.7 Hz, 2H); δ_C (126 MHz; Choloroform-d): 190.63, 162.65, 145.24, 138.63, 132.52, 130.16, 128.57, 128.41, 128.21, 127.79, 124.98, 119.13, 109.85, 71.96, 29.28; HRMS (ESI) calcd for $C_{17}H_{14}O_2$ 251.1072, found 251.1065 $[M+H]^+$.

9b – (*E*)-3-(2,3-dihydrobenzofuran-5-yl)-1-(naphthalen-2-yl) prop-2-en-1-one: pale yellow solid; m.p. 140 °C; FT-IR ν_{max} (KBr; cm^{-1}): 1649.14, 1581.63, 1494.83, 1427.32, 1323.17, 1286.52, 1253.73; δ_H (500 MHz; Choloroform-d): 8.53 (d, *J* = 1.7 Hz, 1H), 8.10 (dd, *J* = 8.5, 1.7 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.94 (d, *J* = 8.6 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 15.6 Hz, 1H), 7.64–7.52 (m, 4H), 7.48 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 4.66 (t, *J* = 8.7 Hz, 2H), 3.28 (t, J = 8.7 Hz, 2H); δ_C (126 MHz; Choloroform-d): 190.36, 162.67, 145.20, 135.96, 135.40, 132.62, 130.21, 129.67, 129.50, 128.49, 128.25, 128.23, 127.86, 127.84, 126.73, 125.05, 124.59, 119.12, 109.88, 77.30, 77.04, 76.79, 71.98, 29.30; HRMS (ESI) calcd for $C_{21}H_{16}O_2$ 301.1228, found 301.1232 $[M+H]^+$.

9c – (*E*)-3-(2,3-dihydrobenzofuran-5-yl)-1-(p-tolyl)prop-2-en-1-one: pale yellow solid; m.p. 135 °C; FT-IR νm_{ax} (KBr; cm^{-1}): 2964.59, 2912.51, 2852.72, 1653.00, 1573.91, 1492.90, 1433.11, 1330.88; δ_H (500 MHz; Choloroform-d): 7.93 (d, *J* = 8.2 Hz, 2H), 7.78 (d, *J* = 15.6 Hz, 1H), 7.53 (d, *J* = 1.9 Hz, 1H), 7.43 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.40 (d, *J* = 15.6 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 2H), 6.82 (d, *J* = 8.2 Hz, 1H), 4.65 (t, *J* = 8.7 Hz, 2H), 3.26 (t, *J* = 8.7 Hz, 2H), 2.43 (s, 3H); δ_C (126 MHz; Choloroform-d): 190.09, 162.53, 144.78, 143.32, 136.00, 130.06, 129.27, 128.56, 128.15, 127.89, 124.94, 119.12, 109.82, 71.93, 29.72, 29.29, 21.68; HRMS (ESI) calcd for $C_{18}H_{16}O_2$ 265.1228, found 265.1223 $[M+H]^+$.

9d – (*E*)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-3-(2,3-dihydrobenzofuran-5-yl)prop-2-en-1-one: yellow solid; m.p. 179 °C; FT-IR $\nu\mu_{ax}$ (KBr; cm^{-1}): 2912.51, 2848.86, 1678.07, 1597.06, 1571.99, 1469.76, 1435.04, 1309.67, 1242.16; δ_H (500 MHz; Choloroform-d): 7.76 (d, *J* = 15.5 Hz, 1H), 7.64–7.56 (m, 2H), 7.52 (d, *J* = 1.8 Hz, 1H), 7.42 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.36 (d, *J* = 15.5 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 4.64 (t, *J* = 8.7 Hz, 2H), 4.36–4.26 (m, 4H), 3.26 (t, *J* = 8.7 Hz, 2H); δ_C (126 MHz; Choloroform-d): 188.61, 162.48, 147.71, 144.47, 143.40, 132.35, 130.02, 128.13, 127.94, 124.89, 122.53, 118.78, 117.96, 117.23, 109.80, 71.92, 64.72, 64.18, 29.29; HRMS (ESI) calcd for $C_{19}H_{16}O_4$ 309.1126, found 309.1121 $[M+H]^+$.

9e – (*E*)-1-(2-chlorophenyl)-3-(2,3-dihydrobenzofuran-5-yl) prop-2-en-1-one: yellow solid; m.p. 105 °C; FT-IR ν_{max} (KBr; cm^{-1}): 3064.89, 2947.23, 2883.58, 1653.00, 1581.63, 1502.55, 1429.25, 1319.31, 1282.66; δ_H (500 MHz; Choloroform-d): 7.47–7.30 (m, 7H), 6.97 (d, *J* = 16.0 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 4.63 (t, *J* = 8.7 Hz, 2H), 3.23 (t, *J* = 8.7 Hz, 2H); δ_C (126 MHz; Choloroform-d): 194.02, 162.98, 146.97, 139.49, 139.38, 131.12, 130.54, 130.22, 129.25, 128.35, 127.26, 126.79, 125.02, 123.53, 109.88, 72.02, 29.19; HRMS (ESI) calcd for $C_{17}H_{13}ClO_2$ 285.0682, found 285.0678 $[M+H]^+$.

9f – (*E*)-1-(3-chlorophenyl)-3-(2,3-dihydrobenzofuran-5-yl) prop-2-en-1-one: pale yellow solid; m.p. 115 °C; FT-IR ν_{max} (KBr; cm^{-1}): 2960.73, 2899.01, 1643.35, 1597.06, 1573.91, 1489.05, 1436.97, 1338.60; δ_H (500 MHz; Choloroform-d): 7.97 (t, *J* = 1.9 Hz, 1H), 7.88 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.80 (d, *J* = 15.5 Hz, 1H), 7.58–7.50 (m, 2H), 7.44 (t, *J* = 7.9 Hz, 2H), 7.33 (d, *J* = 15.5 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 4.66 (t, *J* = 8.7 Hz, 2H), 3.27 (t, *J* = 8.7 Hz, 2H); δ_C (126 MHz; Choloroform-d): δ 189.15, 162.92, 146.09, 140.25, 134.83, 132.42, 130.44, 129.90, 128.49, 128.31, 127.53, 126.46, 125.09, 118.43, 109.92, 77.29, 77.03, 76.78, 72.02, 29.24; HRMS (ESI) calcd for $C_{17}H_{13}ClO_2$285.0682, found 285.0678 $[M+H]^+$.

9g – (*E*)-1-(4-chlorophenyl)-3-(2,3-dihydrobenzofuran-5-yl) prop-2-en-1-one: pale yellow solid; m.p. 169 °C; FT-IR ν_{max} (KBr; cm^{-1}): 2902.87, 2854.65, 1631.78, 1556.55, 1487.12, 1438.90, 1346.31, 1313.52, 1242.16, 1205.51; δ_H (500 MHz; Choloroform-d): 7.95 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 15.5 Hz, 1H), 7.53 (d, *J* = 1.9 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.43 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.34 (d, *J* = 15.5 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 4.65 (t, *J* = 8.7 Hz, 2H), 3.26 (t, *J* = 8.7 Hz, 2H); δ_C (126 MHz; Choloroform-d): δ 189.20, 162.83, 145.74, 138.89, 136.92, 130.30, 129.82, 128.87, 128.28, 127.60, 125.06, 118.48, 109.91, 71.99, 29.25; HRMS (ESI) calcd for $C_{17}H_{13}ClO_2$285.0682, found 285.0675 $[M+H]^+$.

9h – (*E*)-3-(2,3-dihydrobenzofuran-5-yl)-1-(4-fluorophenyl) prop-2-en-1-one: yellow crystals; m.p. 155 °C; FT-IR ν_{max} (KBr; cm^{-1}): 2962.66, 2904.80, 1647.21, 1568.13, 1483.26, 1427.32, 1327.03; δ_H (500 MHz; Choloroform-d): 8.09–8.01 (m, 2H), 7.79 (d, *J* = 15.5 Hz, 1H), 7.54 (d, *J* = 1.8 Hz, 1H), 7.44 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.36 (d, *J* = 15.5 Hz, 1H), 7.17 (t, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.2 Hz, 1H), 4.66 (t, *J* = 8.7 Hz, 2H), 3.26 (t, *J* = 8.7 Hz, 2H); δ_C (126 MHz; Choloroform-d): 188.90, 162.75, 145.45, 134.93, 130.99, 130.91, 130.21, 128.24, 127.66, 125.02, 118.58, 115.74, 115.57, 109.89, 77.28, 77.03, 76.78, 71.98, 29.26; HRMS (ESI) calcd for $C_{17}H_{13}FO_2$ 269.0977, found 269.0979 $[M+H]^+$.

9i – (*E*)-1-(4-bromophenyl)-3-(2,3-dihydrobenzofuran-5-yl) prop-2-en-1-one: yellow solid; m.p. 159 °C; FT-IR ν_{max} (KBr; cm^{-1}): 2968.45, 2910.58, 1649.14, 1579.70, 1489.05, 1431.18, 1330.88, 1242.16; δ_H (500 MHz; Choloroform-d): 8.09–8.01 (m, 2H), 7.79 (d, *J* = 15.5 Hz, 1H), 7.54 (d, *J* = 1.8 Hz, 1H), 7.44 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.36 (d, *J* = 15.5 Hz, 1H), 7.17 (t, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.2 Hz, 1H), 4.66 (t, *J* = 8.7 Hz, 2H), 3.26 (t, *J* = 8.7 Hz, 2H); δ_C (126 MHz; Choloroform-d): 189.39, 162.85, 145.81, 137.34, 131.85, 130.32, 129.95, 128.28, 127.58, 127.55, 125.07, 118.44, 109.91, 77.29, 77.04, 76.78, 72.00, 29.24; HRMS (ESI) calcd for $C_{17}H_{13}BrO_2$ 329.0177, found 329.0172 $[M+H]^+$.

9j – (*E*)-3-(2,3-dihydrobenzofuran-5-yl)-1-(3,4-dimethoxy phenyl)prop-2-en-1-one: yellow crystals; m.p. 156 °C; FT-IR ν_{max} (KBr; cm^{-1}): 3068.75, 2966.52, 2924.09, 2845.00, 1643.35, 1568.13, 1494.83, 1444.68, 1413.82, 1340.53, 1247.94; δ_H (500 MHz; Choloroform-d): 7.79 (d, *J* = 15.5 Hz, 1H), 7.68 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.62 (d, *J* = 2.0 Hz, 1H), 7.54 (d, *J* = 1.8 Hz, 1H), 7.49–7.38 (m, 2H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 4.65 (t, *J* = 8.7 Hz, 2H), 3.97 (s, 6H), 3.26 (t, *J* = 8.7 Hz, 2H); δ_C (126 MHz; Choloroform-d): 188.69, 162.48, 153.05, 149.20, 144.38, 131.70, 129.94, 128.13, 127.96, 124.95, 122.77, 118.70, 110.82, 109.95, 109.82, 71.93, 56.11, 56.08, 29.31; HRMS (ESI) calcd for $C_{19}H_{18}O_4$ 311.1283, found 311.1277 $[M+H]^+$.

9k – (*E*)-3-(2,3-dihydrobenzofuran-5-yl)-1-(3-nitrophenyl) prop-2-en-1-one: brown solid; m.p. 157 °C; FT-IR ν_{max} (KBr; cm^{-1}): 3095.75, 2968.45, 2908.65, 1651.07, 1566.20, 1490.97, 1438.90, 1348.24, 1309.67, 1246.02; δ_H (500 MHz; Choloroform-d): 8.83 (d, *J* = 2.0 Hz, 1H), 8.46–8.40 (m, 1H), 8.35 (m, 1H), 7.87 (d, *J* = 15.5 Hz, 1H), 7.71 (t, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 1.9 Hz, 1H), 7.47 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.39 (d, *J* = 15.5 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 4.68 (t, *J* = 8.7 Hz, 2H), 3.29 (t, *J* = 8.7 Hz, 2H).

9l – (*E*)-3-(2,3-dihydrobenzofuran-5-yl)-1-(2- hydroxyphenyl) prop-2-en-1-one: yellow solid; m.p. 118 °C; FT-IR ν_{max} (KBr; cm^{-1}): 3309.85, 2970.38, 2926.01, 1645.28, 1597.06, 1558.48, 1490.97, 1436.97, 1340.53; δ_H (500 MHz; Choloroform-d): 12.98 (s, 1H), 7.95–7.87 (m, 2H), 7.56 (s, 1H), 7.52 (d, *J* = 15.4 Hz, 1H), 7.50–7.44 (m, 2H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 4.67 (t, *J* = 8.7 Hz, 2H), 3.28 (t, *J* = 8.7 Hz, 2H). δ_C (126 MHz; Choloroform-d): 193.68, 163.56, 163.05, 145.89, 136.10, 130.59, 129.50, 128.36, 127.54, 125.26, 120.18, 118.73, 118.61, 116.91, 109.98, 72.05, 29.23.

5. Conclusions

In summary, the ultrasound-assisted robust protocol reported herein is characterized by short reaction times, an operationally simple method, simplicity of work-up and purification by a simple crystallization method rendering a green approach to synthesize novel (*E*)-3-(2,3-dihydrobenzofuran-5-yl)-1-(aryl)prop-2-en-1-one chalcone derivatives. All the synthesized chalcones are novel (except **9a**) with potential medicinal properties and the strategy is adequate in terms of purity and product yield. Further study is underway to investigate the biological activities of the newly synthesized compounds.

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