Al-imam Muhammad ibn Saud Islamic University
College of Science
Department of Chemistry

Solvent-free Synthesis of Simple Chalcones

A graduation research project

Submitted to the Department of Chemistry in partial fulfillment of the
Requirements for the completion the degree of Bachelor of Science in

By

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List of Abbreviation

FT-IR	Fourier transformer infrared
UV-Vis	Ultraviolet- visible
DSSC	dye-sensitized solar cell
NLO	Nonlinear optical
Et_2O	diethyl ether

List of symbols

E_{opt}	Energy optical band
λ_{onset}	Lambda onset
λ_{max}	Lambda max
eV	Electron volt

Acknowledgment

At the culmination of our graduation project research, we extend our heartfelt gratitude to those who have guided and supported us along this academic journey. We express our deepest appreciation to our research supervisor, Dr.Sondos Almahmoud. Providing us with the knowledge, skills, and guidance necessary to navigate the for the success of our research. We are particularly grateful for the opportunity to visit the central laboratory at Imam Muhammad bin Saud University under your tutelage. Your hands-on instruction has given us a practical understanding of the FT-IR and UV-Vis technique, which has greatly enriched our research experience. We would also like to acknowledge the unwavering support of our parents.

Abstract

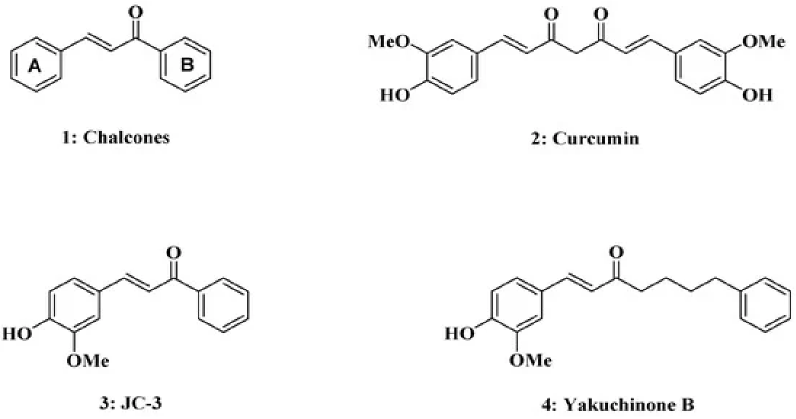
Chalcones are a significant class of organic compounds, forming part of the flavonoid family and distinguished by unsaturated carbonyl system. These compounds are composed of two aromatic rings connected by a three-carbon chain with a double bond, giving them their characteristic reactivity. Chalcones exhibit a wide range of biological activities, including anti-inflammatory, antioxidant, antimicrobial, anticancer, and antimalarial effects. Due to their relatively simple chemical structure, chalcones are easily modifiable, making them a promising scaffold for drug discovery and the development of therapeutic agents. Which inspired the idea of our project to test the conventional preparation technique and the solvent free preparation technique to prepare the chalcone, which was successful in both ways, but the solvent free technique gave the highest yield.

التشالكونات هي فئة مهمة من المركبات العضوية وتُعتبر جزءاً من عائلة الفلافونويد، وتتميز بوجود نظام كربوني مزدوج غير مشبع وتتألف هذه المركبات من حلقتين عطرية مرتبطتين بسلسلة كربونية تتكون من ثلاث ذرات ذات رابطه مزدوجه، مما يكسبها تفاعلية مميزة. تتمتع التشالكونات بمجموعة واسعة من الأنشطة البيولوجية، بما في ذلك تأثيرات مضادة للالتهابات، ومضادة للأكسدة، ومضادة للميكروبات، ومضادة للسرطان، ومضادة للملاريا. وبفضل هيكلها الكيميائي البسيط نسبياً، يمكن تعديل التشالكونات بسهولة، مما يجعلها أساساً واعداً لاكتشاف الأدوية وتطوير العوامل العلاجية، وأدى ذلك إلى فكرة المشروع بحيث حضرنا المركب بالطريقة التقليدية وبالطريقة الجافة، ووجدنا أن الطريقتين فعالتين، ولكن كانت الطريقة الجافه ذات ناتج اعلى.

1. Introduction

1.1 Historical background

Chalcones are natural compounds consisting of two aromatic rings linked together by a three-carbon unsaturated carbonyl bridge. It is one of the most characterized scaffolds in medicinal chemistry that can be synthesized in vitro and can be converted into therapeutically active heterocyclic scaffolds. It also plays a major role in non-pharmaceutical scientific applications; (Figure1) show the chalcone general structure.[1]



1: Chalcones

2: Curcumin

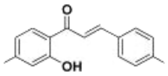
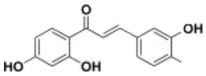
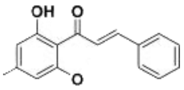
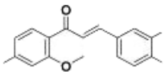
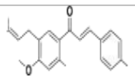
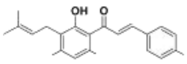
3: JC-3

4: Yakuchinone B

Figure 1 chalcones general structure.

1.2. Chalcones sources in nature

Chalcones are considered essential cores for many interesting compounds from natural sources. As in many articles, the term “chalcone” refers to chemicals with an α, β-unsaturated ketone system. In general, the chalcones family is classified into two categories: simple chalcones and hybrid chalcone with the core scaffold of 1,3-diaryl-2-propen-1-one. The following (Table 1) shows examples of natural chalcones obtained from natural sources. [2]

Entry	**Name**	**Structure**	**Activity**	**Natural source**
Classical chalcones.				
1	Isoliquiritigenin		Anti-cancer Chemopreventtive Antioxidant Anti-inflammation	Nepalesepropolis
2	Butein		Anti-cancer Ati-inflammation	Rhus verniciflua
3	Cardamonin		Schistosoma Mansoni ATP diphosphohydrolase	Piper aduncum L.
4	Sappanchalcone		Anti-inflammation	Sappan Lignum
5	bavachalcone		Anti-bacterial	Psoralea Corylifolia
6	Morachalcone A		Cytotoxicity	Maclura Pomifera
7	Xanthohumol		Anti-HIV-1 Anti-bacterial Anti-cancer	Hops Humual Lupulus/Angel Keiskei/koidzumi

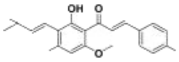
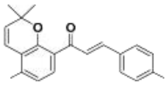
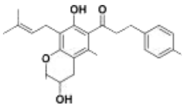
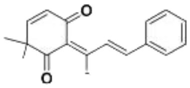
8	Candidachalcone		Estrogenic activity	Tephrosia Candida
9	Millepachine		Anticancer	Millettia
10	Fleminchalcone. A		Tyrosinase inhibitor	Flemingina Philippinensis
Chalcone mimcs/Fused chalcones				
11	Schefflerichal-con		Non-toxic	Uvaria Scheffleri

Table 1 of chalcone natural sources.[2]

1.3. Chalcones Activities

As mentioned above chalcones can be utilized as an intermediate for synthesizing heterocyclic compounds. Chalcone derivatives are studied mostly because it has been found that these derivatives have a wide range of biological activities and has been amazingly effective and useful as a local antibacterial, anticancer, and antifungal agent and more. The following diagram shows the main activities of chalcones (Figure 2) along with other chalcones anti stuctures shown in(Figure 3). [3]

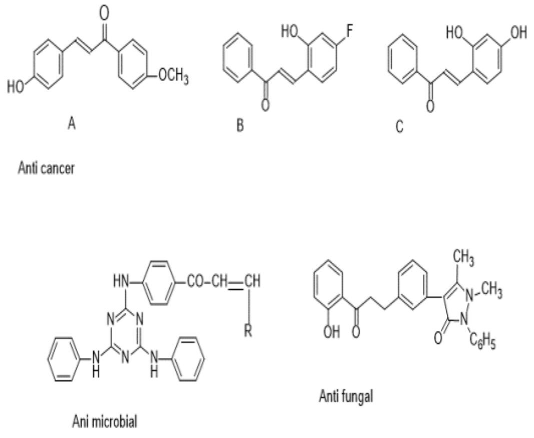


Figure 3 chalcone Anti stractur

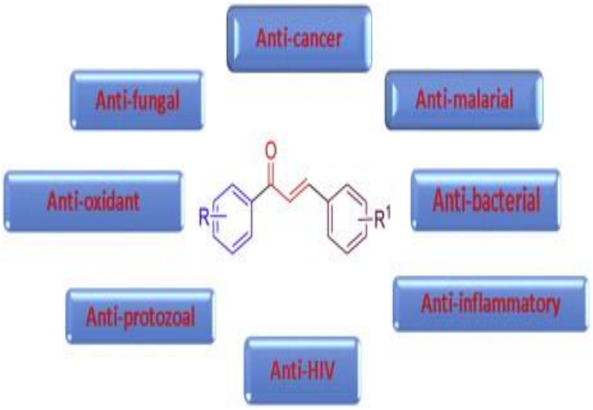


Figure 2 many activities of chalcones. [6]

1.4. Preclinical pharmacological

Chalcones have many beneficial properties including anti-inflammatory, antimicrobial, antioxidant, anticancer, anti-amyloid, ant diabetic, anti-obesity, lipid lowering and cytoprotective. Chalcone derivatives exert hepatoprotective action in non-alcoholic fatty liver disease, alcoholic fatty liver, drug and toxin-induced liver injury and hepatocellular carcinoma through several mechanisms. Chalcones regulate adipocyte function and adiponectin secretion. They also inhibit the production of triglycerides; hepatic stellate cell activating factors and extracellular matrix deposition and increase fatty acid oxidation. These actions of chalcone lead to the improvement of liver injury. In conclusion, chalcones reduce liver injury markers and histological abnormalities in liver injury. [4]

1.5. Chemical reactions of chalcones

Chalcones are good precursors for further organic compounds and pharmaceuticals. Below are some examples on chalcones reactions. [5]

- Oxidation of chalcones:

The oxidation of chalcone is a chemical reaction where chalcone undergoes an increase in oxidation state and resulting in formation of new compounds such as epoxides, or dihydrochalcones. Example: oxidations of chalcone to epoxide using reagents like hydrogen peroxide (H_2O_2) in the presence of base or other oxidizing agents shown in (Figure 4).[5]

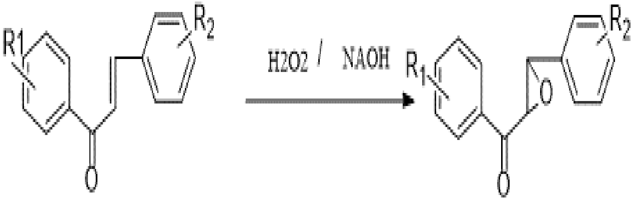


Figure 4 oxidation of chalcone

- Cyclisation reaction of chalcones

The Cyclization of chalcone is a chemical reaction where a chalcone undergoes intermolecular transformation to form cyclic compounds,this process often involves an enzyme like chalcone isomers which leads to the conversion of linear chalcone into more stable ring form,such as flavanones. Example: chalcone to flavanone cyclization , reaction of chalcone with dinucleophile to form heterocyclic rings as shown below in (Figure 5). [6–8]

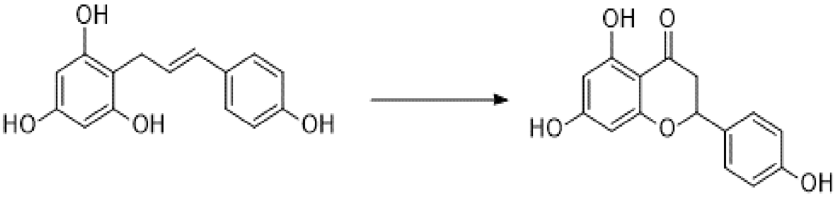


Figure 5 Cyclisation reaction of chalcones

- Reduction reaction of chalcones

The reduction reaction of chalcone typically involves converting unsaturated ketone through catalytic hydrogenation, or enzymatic reductiont depending on reducing agent used. This reaction results in the saturation of the double bond in chalcone structure for example: formation of dihydrochalcon as shown below in (Figure 6) . [9],[10]

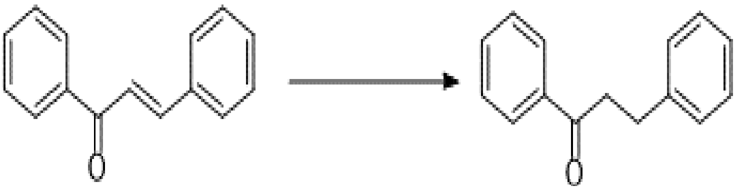


Figure 6 Formation of dihydrochalcone

1.6. Application of chalcone

Chelcones and their derivatives have large significance in medicinal chemistry due the broad spectrum of the therapeutic potential and pharmacological properties, such as anticancer, antibacterial, anti-inflammatory antimicrobial..etc.[11] Chalcones used in agricultural applications for phytotoxic activities to develop new herbicides. [12] They can be used in different optoelectronic applications including dye-sensitized solar cell (DSSC). Chalcone and derivatives are widely used in nonlinear optical (NLO), optical computing and photo initiated polymerization. [13]

1.7. Synthesis of chalcones

The synthesis of chalcones are considered extremely simple and straightforward.[14]Chemically, chalcone based compounds can be synthesized to produce a variety of compounds with different structures. This is one of the main advantages of chalcone compounds. [15] There are many processes used to synthesize different derivatives of chalcones. Usually, condensation procedures are used in the presence of base or acid catalyst. The main routes for the synthesis of chalcones include Claisen–Schmidt condensation, however, the carbonylative Heck coupling reaction, coupling reactions, Sonogashira isomerization coupling, Meyer–Schuster rearrangement, Suzuki–Miyaura coupling reactions, Suzuki coupling reactions, Stille coupling, can also be used and(Figure 7)shows examples of chalcones synthesis. [16]

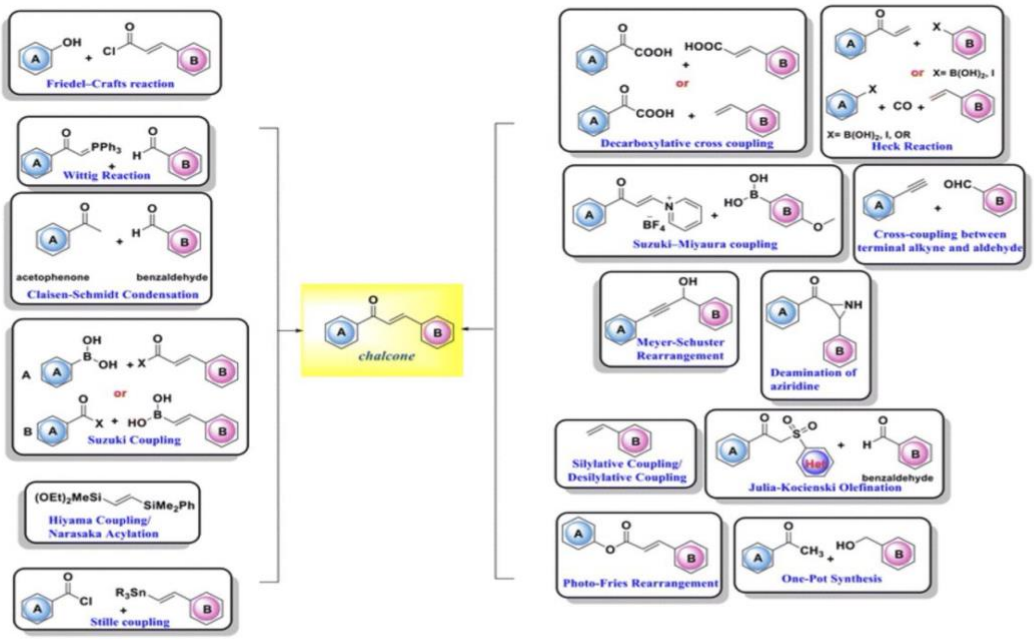


Figure 7 example for synthesis of Chalcone [16]

1.7.1. Conventional synthesis

A substance in which solute is dissolved and forms solution is a solvent. Generally solvent is a liquid but it can also be a solid, a gas, or a supercritical fluid. For example of a solvent that is proven effective is ethyl alcohol, chalcone derivative were synthesis via treatment of acetophenone and benzaldehyde derivative in equal amount using ethyl alcohol in 40% NaOH solution ,the reaction proceeded via Claisen -Schmidt reactions. [15]This interaction is the one used in our research.

1.7.2 Solvent –free synthesis

The first principle of green chemistry is to prevent waste , and the reduction of auxiliary material as solvent and reduced in their toxicity ,though is not easy control of organic reaction without solvent, but can used eco-friendly solvent that own this definition to environment reasons, low cost ,time and energy waste.[17] Further, most of the organic solvents are considered as hazardous materials to humans and the environment.[14] The solvent-free synthesis depends on a physical mixing both starting materials, the aldehyde and ketone without using solvents. This physical mixing creates enough energy to activate the reaction, so it does not require any heating. [18] The solvent-free was used to prepared 20 compounds of chalcone by grinding the benzaldehyde (unsubstituted, 4-methyl, 4-methoxy, 3-chloro, or 4-chloro) and the acetophenone ((unsubstituted, 4-methyl, 4-bromo, or 4-methoxy) with solid sodium hydroxide using mortar and pestle. This method results in chalcone-based compounds with high purity and high yield.[19] However, a common association between solvent free synthesis and mechanochemical techniques, by using high-speed ball milling, which is used for preparing chalcones and chalcone derivatives. This has decreased the consumption of high cost catalysts and reduce the reaction times. [17]

2. Experimental

2.1. General Experiment

UV-VIS measurements were carried out using SHIMADZU UV-26001 and FTIR measurements were performed using AGILENT 630. Reactions were carried out at room temperature, which refers to 20-25°C. Chemical structures were drawn by Chem Draw ultra. UV-VIS 10 and FTIR spectra were drawn using Excel.

2.2.1 Conventional Synthesis

SSM-1

To a mixture (0.4ml, 3.3 mmol) of Acetophenone and (10ml) of ethanol as a solvent was added (0.2 g) of sodium hydroxide (NaOH).Then, Methoxy benzaldehyde (0.4 ml, 3.3 mmol) was added. The resulting yellow solution was stirred for 3 hours. After the reaction mixture was poured into ice-cold water, diluted HCl neutralized it until PH adjust to 7. Then, organic compound was separated using liquid-liquid extraction used diethyl ether (Et_2O) and dried over calcium chloride (CaCl). The solvent was then evaporated and left to dry at room temperature overnight. The final precipitate was washed with diethyl ether to remove the impurity to yield yellow solid (0.1g, 12.5%). (69.5m. p). FTIR (ν, cm^{-1}):1460(Csp2-H str.), 1590 (C=C str.), 1725(C=O str.),1200(C-O str) . (Figure 11)

SSM-2

To a mixture (0.4ml, 3.3mmol) of Acetophenone and (10ml) of ethanol as a solvent, was added (0.2 g) of sodium hydroxide (NaOH). Then, 4 - (Dimethyl amino) benzaldehyde (0.5 g, 3.3 mmol) was added. The resulting orange solution was stirred overnight at room temperature and was the formed precipitate. After the reaction mixture was poured into ice-cold water, diluted HCl neutralized it until PH adjust to 7. Then, filtered to yield orange solid (0.44g, 53 %.). (96.85m. P). FTIR (*v*, cm^{-1}):1340(Csp2-H str.), 1570 (C=C str.), 1700(C=O str.),1300(C-N str.) (Figure 13)

2.2.2 Solvent Free Synthesis

SSM-1

In a mortar and pestle Acetophenone (0.4ml, 3.3mmol) and Sodium hydroxide (0.2 g). Were ground with 4-methoxybenzaldehyde (0.4ml, 3.3mmol) was added. The resulting mixture was ground for twenty minutes until yellow color appears. The mixture was covered to dry for two hours. Then, to the dry reaction mixture ice-cold water added and the solution . Then, the organic compound was separated using Liquid-liquid extraction. The solvent was evaporated and, left to dry overnight at room temperature to yield a yellow solid (0.35g) (43.13%). (67.5m. P). FTIR (*v*, cm^{-1}):1460(Csp2-H str.), 1590 (C=C str.), 1725(C=O str.), 1200(C-O str) . (Figure 12)

SSM-2

In a mortar and pestle, Acetoohenone (0.4, 3.3mmol) and sodium hydroxide (0.2g) were ground with 4 - (Dimethyl amino) benzaldehyde (0.5g, 3.3mmol) was added. The resulting was ground for five minutes until orange color appears. The mixture was covered to dry. Then, to the dry reaction mixture ice-cold water added and the solution diluted HCl neutralized it until PH adjust to 7. Then filtered and, left to dry overnight at room temperature to yield an orange solid

(0.4gm) (48.78%). (92.1m. P). FTIR (*v*, cm^{-1}):1340(Csp2-H str.), 1570 (C=C str.), 1700(C=O str.), 1300(C-N str.) . (Figure 14)

3. Aim

Our research aims to synthesize chalcones using both conventional method and solvent-free method. We also aim to compare between the two in terms of time, yield and simplicity methods. The target Chalcones (Figure 8) were chosen because they are easy to prepare with different methods.

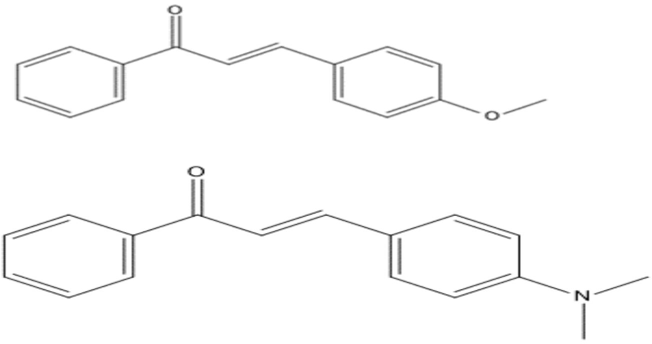


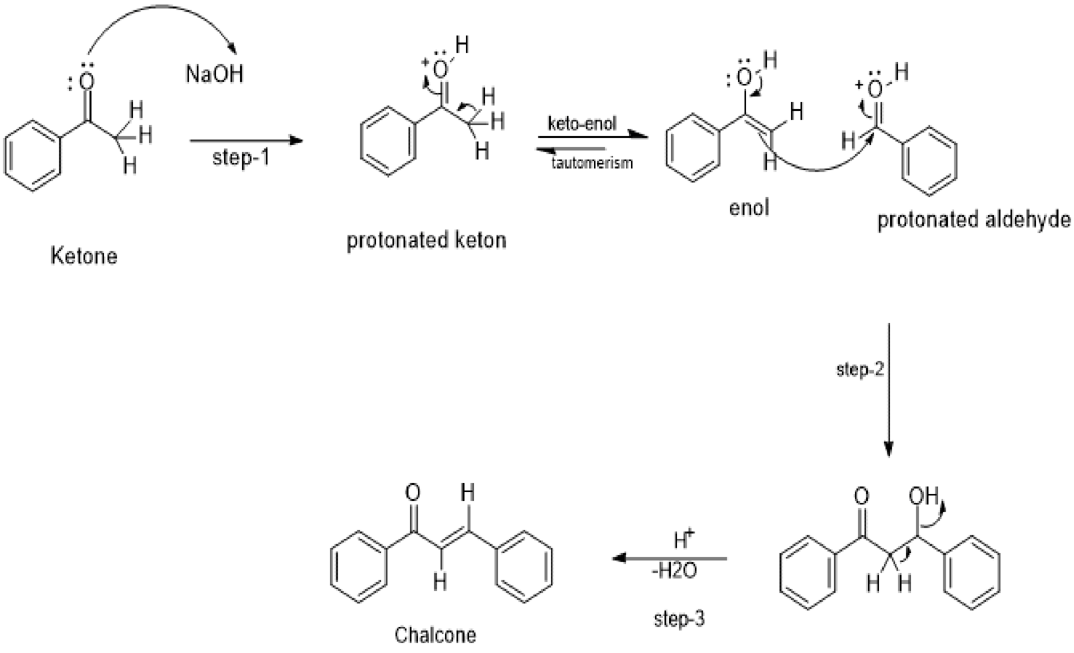
Figure 8 SSM1, SSM2

4. Result and dissociation

4.1 Synthesis

When the target compounds prepared the product with the conventional method, the yield was 53% for SSM-2, and 12% for SSM-1. While the yield of the solvent free method. For SSM-2 was 48.78% and for ssm-1 is 43.13%. It is clear that the yield was slightly higher in solvent free synthesis. Claisen reaction is a condensation reaction of Aldehyde or Keaton in the presence of strong base leading to the product of carbon-carbon bond. In this preparation, the first step is the reaction of the ketone with NaOH, a protonated ketone is formed. In the second step, the reaction of the enol with the protonated aldehyde. In the third step, the ionization stage and the release of water, a chalcone compound is formed, the mechanism of Claisen-Schmidt happens through the following steps: the first step is Deprotonation; a base (e.g., OH^{-}) abstracts a proton

from the alpha carbon of a ketone or aldehyde, generating an enolate ion. Then, the second step is Nucleophilic Attack, the enolate ion then attacks the carbonyl carbon of another molecule of aldehyde or ketone, forming a β-hydroxy ketone (aldol product). The last step is the Dehydration under basic conditions, the β-hydroxy ketone undergoes elimination of water, leading to the formation of the α,β-unsaturated carbonyl compound, i.e., chalcone. [14]
(Scheme 1)Shows the general mechanism.[14]



Scheme 1 Genaral mechanism of Claisen-Schmidt

4.2 Structural Characterization

The compounds were characterized using FTIR spectroscopy which is very useful for identifying the major functional groups in organic compounds. And to establish that the starting materials is no longer present. As shown in Figure (11-14) the detected band in the range of(1725cm^{-1}), and (1690cm^{-1}) for (SSM-1), and (SSM-2) respectively is assigned for the stretching vibration of carbonyl compound that was shifted to lower wave number due to the extended conjugation. In al spectra the peaks related to 4-methoxybenzaldehyd and 4-dimethylaminobenzaldehyd are no longer present which indicates the consumption of our starting material.[20]

4.3 Optical properties

(Figure 9),(Figure 10) shows the UV-Vis absorption spectra of SSM-2-solvent, SSM-2-dry and SSM-1-solvent, SSM-1-dry which were recorded in ethanol solution ($1x10^{-5}M$) SSM-1-solvent, and SSM-1-dry have a similar absorption profile as shown in (Figure 10) and also for SSM-2-solvent, and SSM-2-dry shown in (Figure 9). As you can see in (Table 2), (λ_{onset}) is 408 nm for SSM-1-solvent, and (493nm) for SSM-2-solvent. From solution, measurements (λ_{max}) were found to be in the UV region at 334nm, 338nm for SSM-1, and 416nm, 414nm for SSM-2. Although SSM-1 is more conjugated than SSM-2. The energy band gap (E_{opt}) calculated from (λ_{onset}) were found to be 3.04ev, 2.52ev for SSM-1-solvent, SSM-2-solvent, respectively. As explained above There is no difference in absorption profile for SSM-1, and SSM-2 which means that the dry method and traditional method succeeded and produced the same compound in .

compound	λ_{max}	λ_{onset} (nm)	E_{opt} (ev)
SSM-1-solv	334	408	3.04
SSM-1-dry	338		
SSM-2-solv	416	493	2.52
SSM-2-dry	414		

Table 2data of optical properties

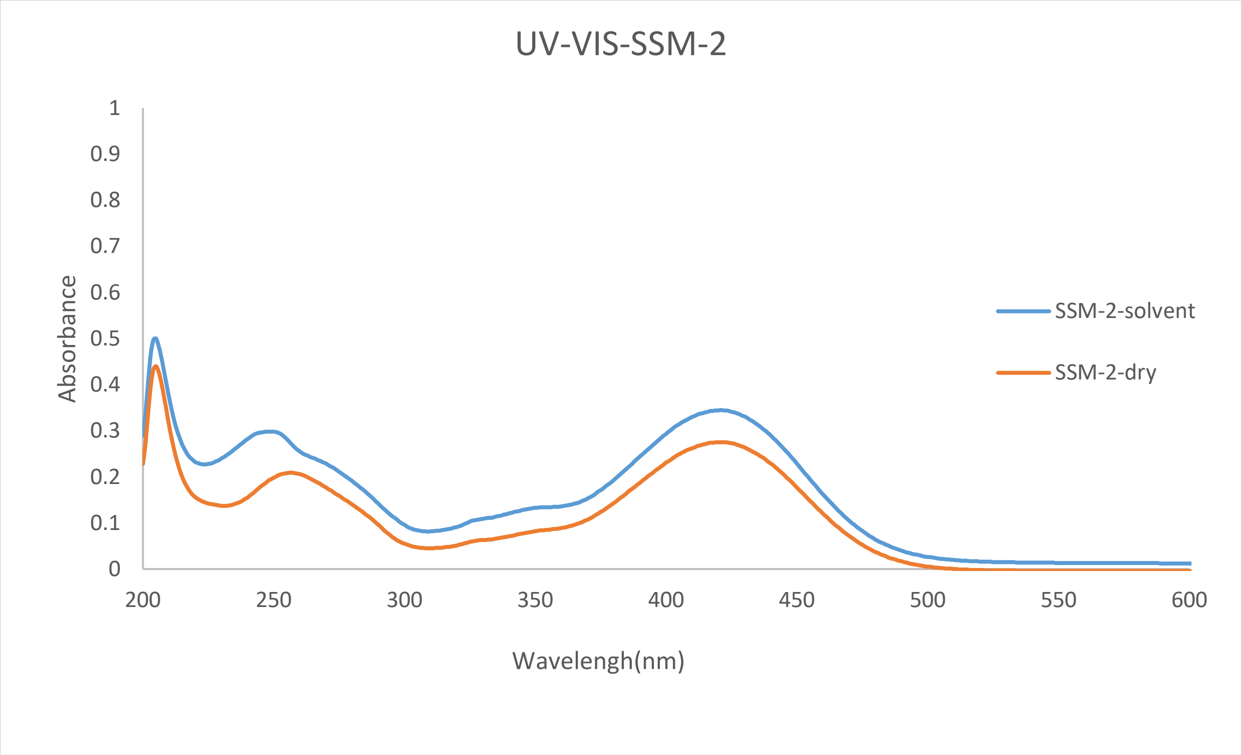


Figure 9 UV-VIS absorption of SSM-2

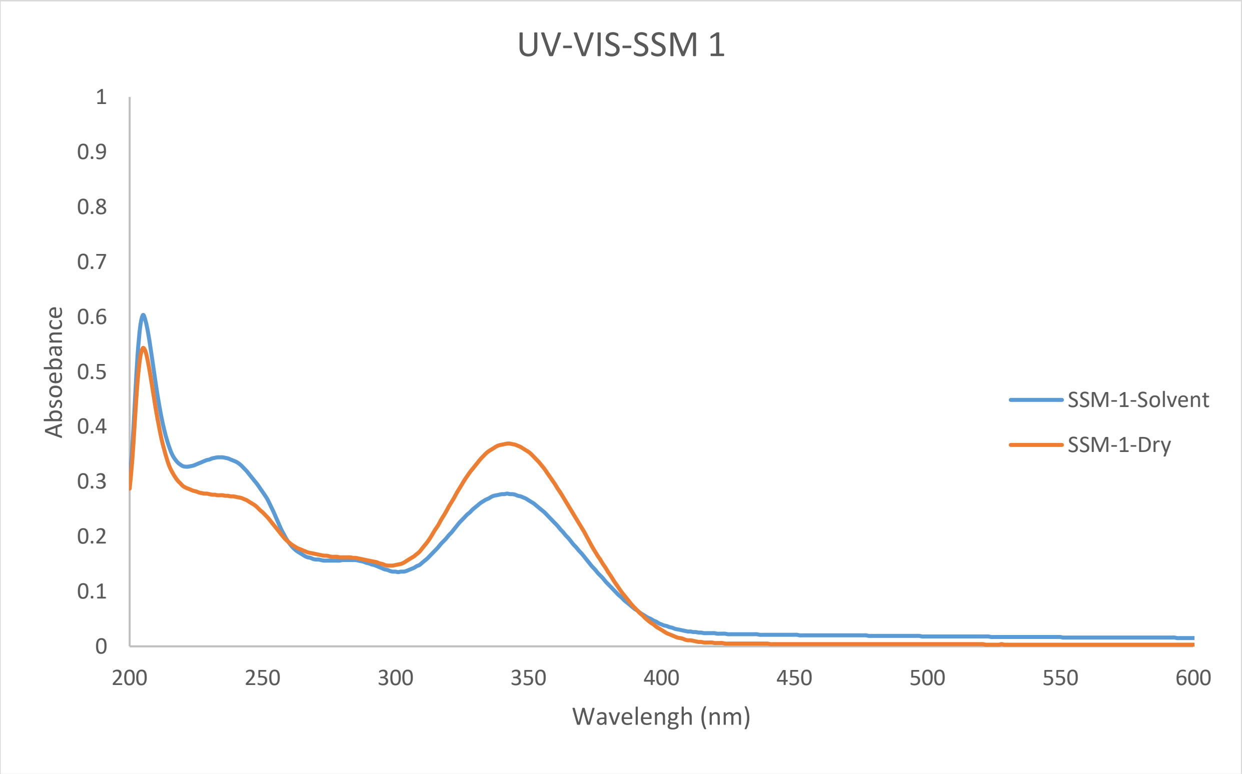


Figure 10 UV-VIS absorption of SSM-1

5. Conclusion

In this study, we successfully synthesized chalcone compounds using both conventional and solvent-free methods. Our findings indicate that the solvent-free method is not only more environmentally friendly but also simplifies the procedure, reducing the time required for the synthesis. We observed that chalcones synthesized via the solvent-free method showed similar properties to those prepared conventionally, making this method a viable alternative for future applications in green chemistry. The optical properties of the compounds were analyzed, and results show variations in their energy band gaps, with SSM-1-solvent having the widest band gap, suggesting potential use in various optical and electronic applications. Overall, this research contributes to more sustainable and efficient methods for synthesizing important organic compounds like chalcones.

6. Recommendation

We recommend that the preparation technique should be applied to a large number of compounds possible for demonstrating the effectiveness and to develop this technique.

7. Reference

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8 .IR Spectrum

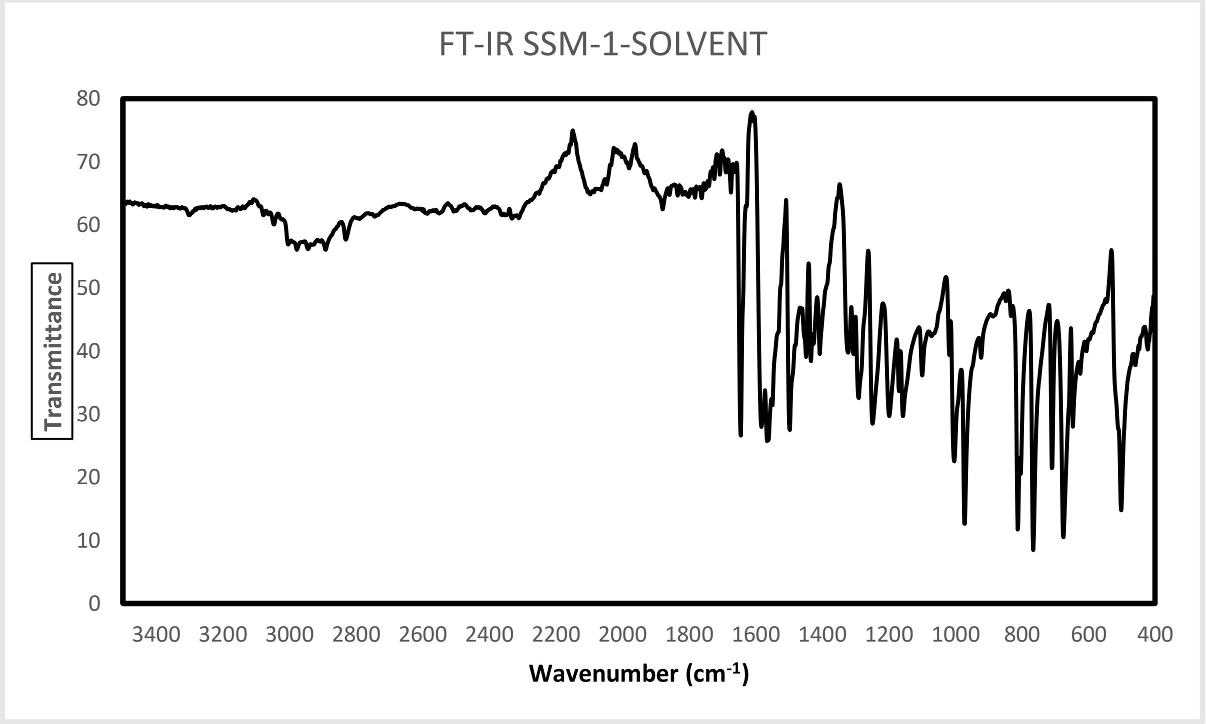

Figure 11 IR spectrum of SSM-1- solvent

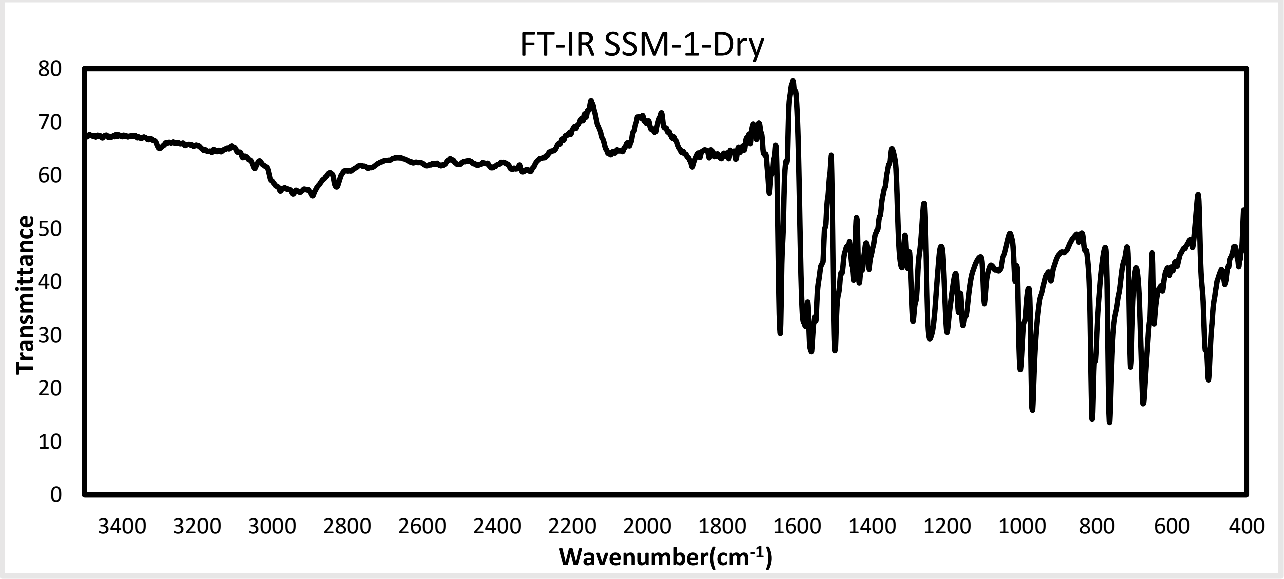

Figure 12 IR spectrum of SSM-1-Dry

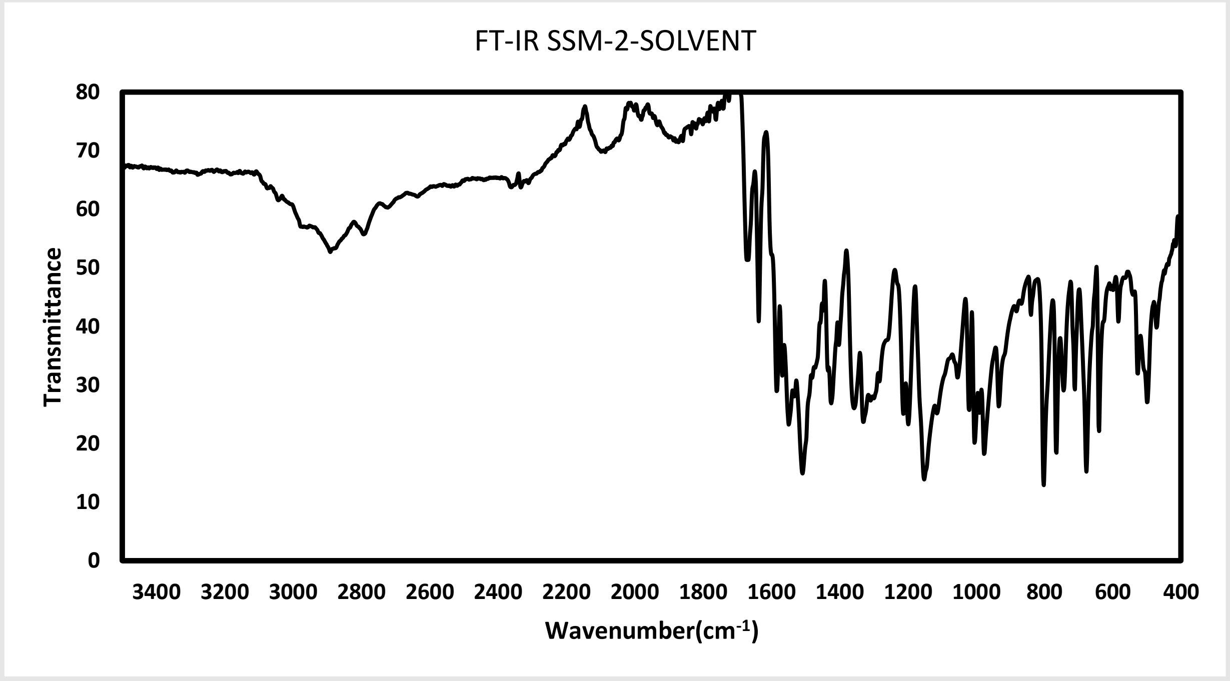

Figure 13 IR spectrum of SSM-2- solvent

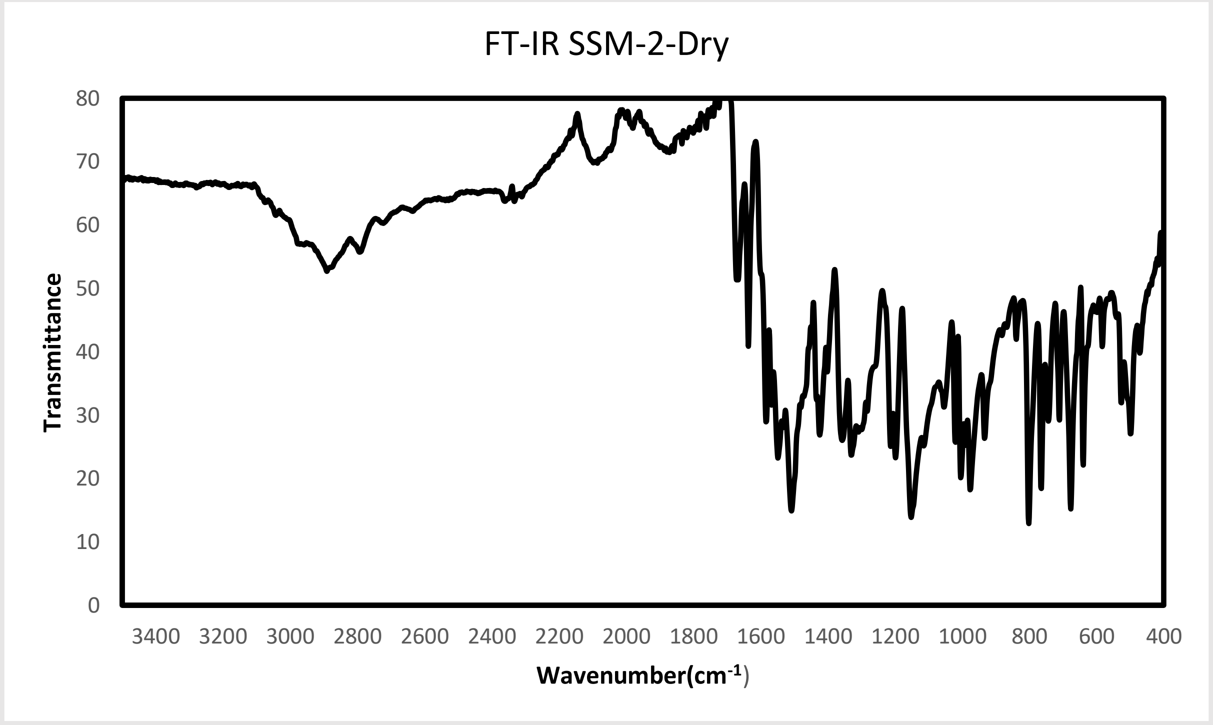

Figure 14 IR spectrum of SSM-2-Dry