Faculty of Resource Science and Technology

ETHERIFICATION STUDIES ON CHALCONE DERIVATIVES WITH SERIES OF BROMOALKANE 1

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Bachelor of Science with Honors
(Resource Chemistry)
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This dissertation is submitted in partial fulfillment of requirements for the degree of Bachelor of Sciences with Honors (Resource Chemistry)

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ABSTRACT

This research is focusing on the etherification studies of chalcone derivatives with series of bromoalkanes which are bromohexane ($C_6H_{13}Br$), bromoheptane ($C_7H_{15}Br$), bromooctane($C_8H_{17}Br$), and bromononane ($C_9H_{19}Br$). There are two different strategy used in this research. The first strategy involved the etherification of 4-hydroxybenzaldehyde followed by synthesis to chalcone derivatives.The second strategy was the synthesis of chalcone using 4-hydroxybenzaldeyde as a starting material followed by etherification to chalcone derivatives. From this research the first strategy give the highest yield.
Key words: etherification, chalcone,antibacterial.

ABSTRAK

Projek ini memfokuskan tentang kajian eterifikasi terhadap sebatian kalkon dengan siri bromoalkana yang terdiri daripada bromoheksana ($C_6H_{13}Br$), bromoheptana ($C_7H_{15}Br$), bromooktana ($C_8H_{17}Br$), and bromononana ($C_9H_{19}Br$). Terdapat 2 kaedah berlainan yang digunakan di dalam kajian ini. Kaedah yang pertama ialah eterifikasi 4-hidroksibenzaldehid diikuti dengan sintesis kalkon. Kaedah yang kedua melibatkan sintesis 4-hidroksikalkon menggunakan 4-hidroksibenzaldehid sebagai bahan pemula diikuti dengan eterifikasi kepada sebatian kalkon. Melalui kajian ini, didapati kaedah yang pertama memberikan hasil produk yang lebih tinggi.
Kata kunci: eterifikasi, kalkon, antibacterial

CHAPTER 1

INTRODUCTION

1,3-diphenyl-2propen-1-one is an aromatic ketone, which are known as chalcone (Figure 1). Other name for this compound is benzalideneactophenone or phenyl styrl ketone. Chalcone can be classified into 3 different group named regular chalcone, chalcone having ß-oxygenation and retrohalcone (Harbone, 1974). Basic structure is **1** (Figure 1).

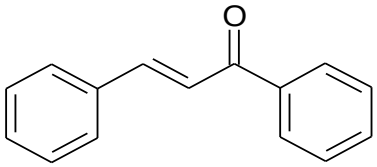

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Figure 1

Chalcone are considered as minor flavonoids, and become the most important intermediates in the biosynthesis of flavonoids (Roux and Ferreira: 1974; Ali and Kagan: 1974). Chalcone and its derivatives are known to have various pharmacological activities such as anti mitotic which have the cell growth inhibitory properties (Ducki et al., 1998). Chalcone also used as the inhibitor on some specific enzyme, stabilization agent for heating process and make use as pigment colours in colour photography field (Dhar,1981). According to Steenkamp, 2003 *Agapanthus African* that composed of two chalcone units is used as a traditional medicine by African women to induce and to treat the constipation during the pregnancy.

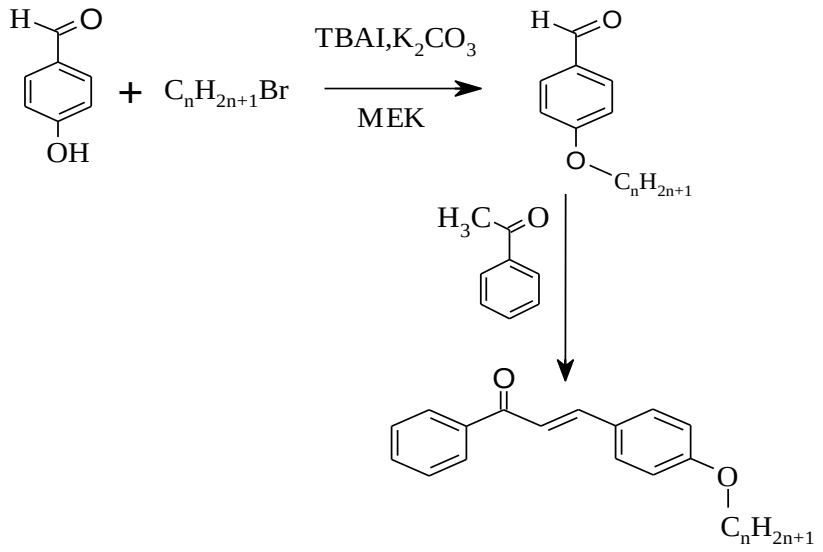
Chalcone bearing non-constituents also have been synthesized in order to develop drug active against cancer, tuberculosis, and cardiovascular diseases (Eddarir et al., 2003). In 2002, Rojas et al., state that chalcone possess antibacterial activity. Thus research has been done to investigate this property. According to Selvakumar et al., 2007, several compound possessing chalcone were synthesized and tested for antibacterial activity.

In this research, 4-hydroxybenzaldehyde was used as a starting material. There were two different types of strategies that have been used to conduct this research using different series of bromoalkane. The series of bromoalkane consist of bromohexane ($C_6H_{13}Br$), bromoheptane ($C_7H_{15}Br$), bromooctane ($C_8H_{17}Br$), and bromononane ($C_9H_{19}Br$). FT-IR and NMR instrumentation have been used to determine the functional group exist in the synthesized compound.

The main objectives of this research are;

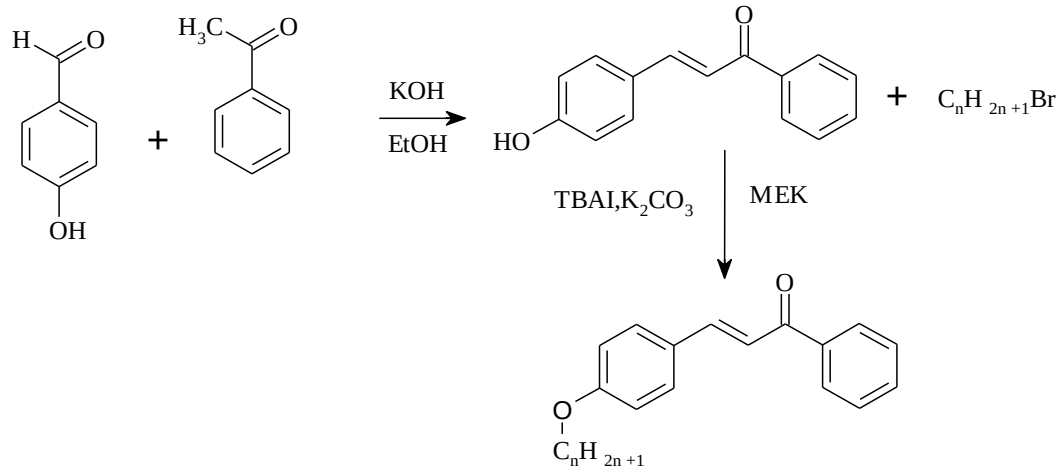
1) To synthesis the chalcone derivatives through etherification with two different strategy (Scheme 1 and Scheme 2) and determine the strategy that produced high yield of chalcone derivatives by comparing the yield percentage.

Strategy 1: Etherification Process Followed by Synthesis of Chalcone



Scheme 1

Strategy 2: Synthesis of chalcone followed by etherification process



Scheme 2

2) To determine whether the etherified chalcone will show antibacterial properties through bioassay study.

CHAPTER 2

LITERATURE REVIEW

2.0 Chalcone extracted from Plants

There are many species of plant that can be extracted which contain chalcone. In the investigation of chalcone from the seed of *Cedrelopsis grevei* (Ptaeroxylaceae), 5 different type of chalcone derivatives and dihydrochalcone was isolated. One of the compounds found which is cedrediprenone **2** (Figure 2) presents as a yellow crystalline material after isolated. It was known to be an active at inhibiting the luminol–enhanced chemiluminesence of reactive oxygen metabolites produced by human polymorphonuclear leucocytes activated with opsonized zymosan. Another importance of this compound was to scavenge superoxide anions in a cell free system. (Smit et al., 2000 and Van den Worm, 2001).

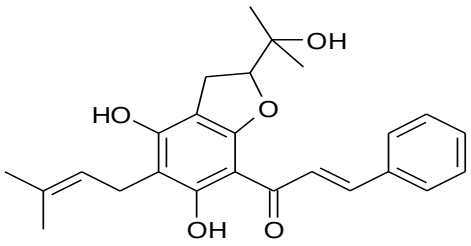


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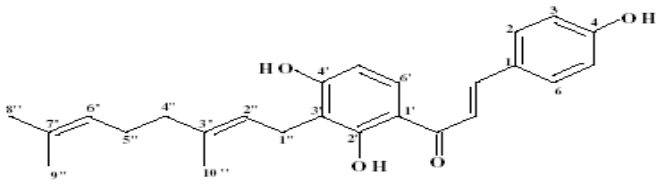
Figure 2

Another investigation was carried out on *Artocarpus nobilis* plant *found* from the central of Sri Lanka. In this investigation, 5 different types of chalcone derivatives **3**, **4**, **5**, **6**, and **7** (Figure 3) were reported after isolation and structure elucidation.

All of these compounds showed good antifungal activity against *Cladosporium cladosporioides* and high radical scavenging activity (Jayasinghe et al., 2004)



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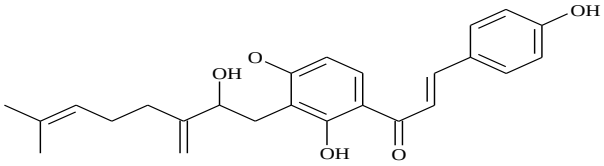

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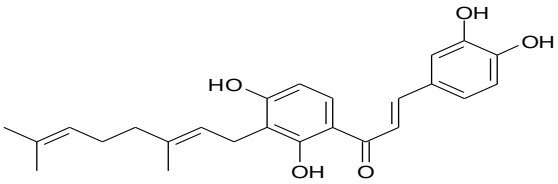

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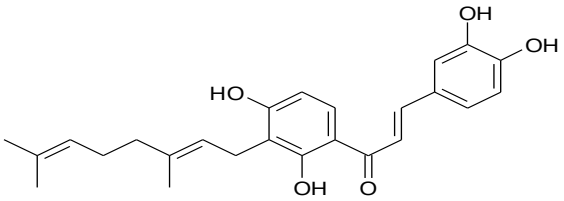

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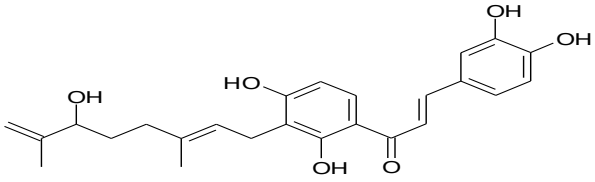

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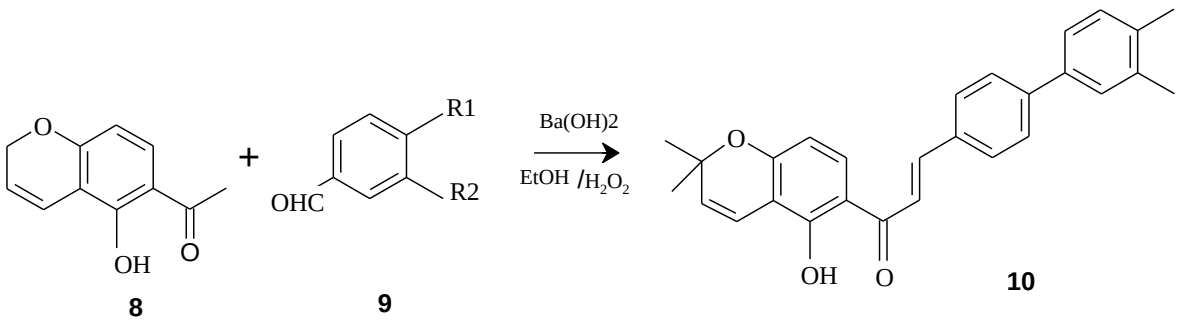
Figure 3

2.1 Synthesis of Chalcone derivatives

There are several methods have been used to synthesis chalcones. According to Dhar, 1981 chalcone can be synthesised through the reaction between acetophenone and benzaldehyde in the presence of base. Through this method, acetophenone in ethanol is mixed with benzaldehyde in ethanol and this mixture was treated in an aqueous solution of potassium hydroxide (KOH). This reaction is known as Claisen Schmidt condensation reaction.

This reaction proved when Sathyanarayana and Krishmuty, 1988 using Claisen Schmidt condensation reaction method to synthesis chalcone derivatives **10**. In this research, 2'-hydroxychalcone with a variety of substitution patterns have been synthesized in excellent yields (75%-90.5%). This reaction is using aldehyde **8** with hydroacetophenones **9** in the presence of partially dehydrated barium hydroxide Ba $(OH)_2.5H_2O$ (Scheme 3)

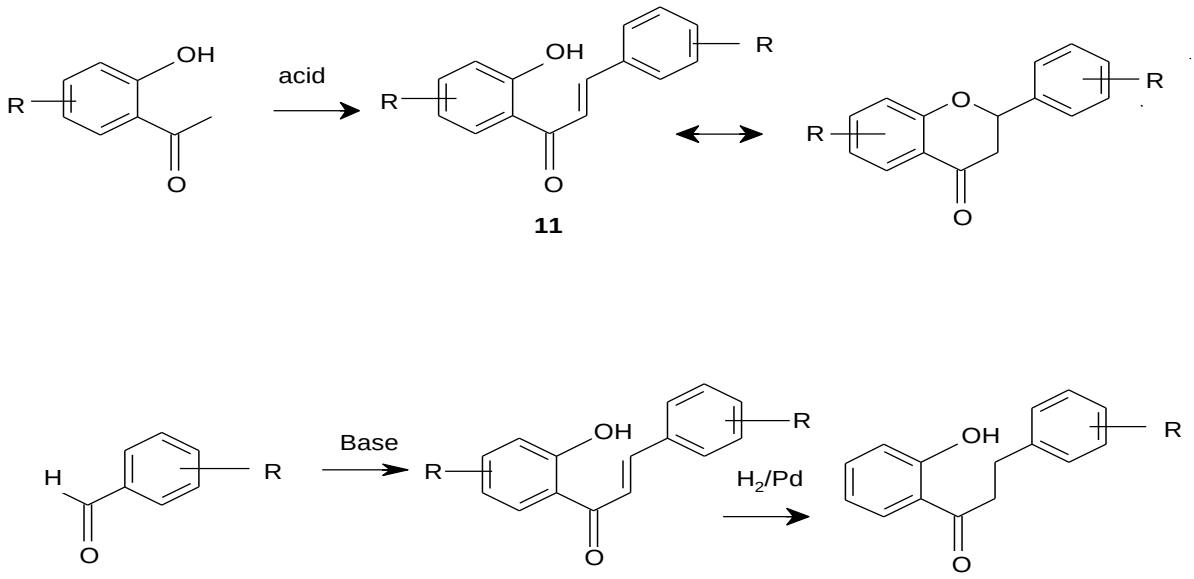


Scheme 3

Chalcone synthesis can also be synthesized in acidic and basic condition. A research have been done to prepare chalcone are readily accessible through two well established routes which comprise a base catalyzed aldol condensation and acid mediated aldolization (Von Konstanecki and Rossbach, 1896; Augustyn et al., 1990).

According to Herdan and his coworkers in 1990, they find out that the synthesis of a small series of chalcone **11** (Scheme 4) give better yield under acidic condition. The yield was 75% - 80%. According to Marais et al., 2005 the base catalyzed aldol condensation represents a more feasible routes toward chalcone because the acid protocol is prone to subsequent cyclization to afford the corresponding racemic flavones.

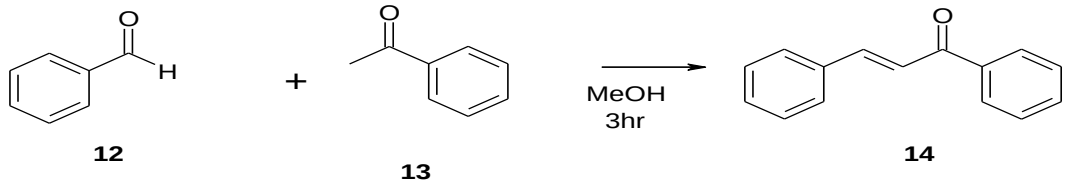
In 2002, Choi and Cha managed to synthesis chalcone using a mixture of 4-hydroxybenzaldehyde acetophenone dissolved in ethanol. This reaction was cooled and added with sodium hydroxide. The yield for the product is 70%. Based on research by Wu et al., 2005 they were managed to synthesize a series of ferrocenyl chalcone which contribute to the antiplasmodial activity. He and his co-workers applied the Claisen-schmidt reaction in base catalyzed to synthesis ferrocenyl chalcones.



R=OH,OMe,OBn, OMOM ,etc

Scheme 4

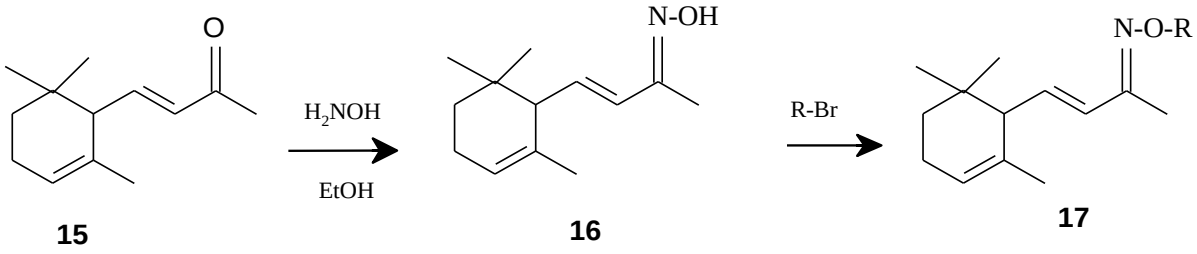
The Claisen-Schmidt condensation reaction proposed by Lin et al., 1977 has been adopted by Sivakumar and his co workers in 2007 for the preparation of twenty five chalcone derivatives **14** (Scheme 5). Aldehyde **12** and acetophenone **13** derivatives were added and stirred in methanol at room temperature. When natrium hydroxide (NaOH) was added under rapid stirring to the above mixture more than 80% was obtained.



Scheme 4

2.2 Etherification Study

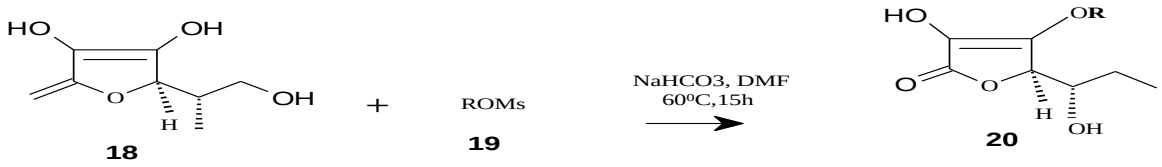
Banerjee and Dureja, 2005 reported the synthesis of oxime ether through etherification. In this research, α-ionone compound **15** reacted with hydroxyl amine to produce 4'-(2,6,6,trimethyl-2-cycloxen-1-yl)-3'-buten-2'-ketoxime, compound **16**. The 4'- (2, 6, 6-trimethyl-2-cyclohexen-1-yl)-3'-buten-2'-ketoxime was then reacted with an appropriate alkyl halide to give the oxime ethers, **17** as shown in Scheme 6. This research has been done to study the oxime ethers group which is important in endocrine system of an insect. Among the oxime ether group of insect, growth regulators acetaldoxime ether showed high activity against M. domestica (Henrick et al., 1973)



R = CH_3, C_2H_5, C_3H_7, $CH(CH_3)_2$, C_4H_9, $CH_2CH(CH_3)_2$, C_5H_{11}, $C_2H_4CH(CH_3)_2$, C_6H_{13}, C_7H_{15}, C_8H_{17} and $C_{10}H_{21}$.

Scheme 6

Another research have been done using etherification was done by Beifuss et al., 2000.This research used direct alkylation of $_{L}$-ascorbic acid (Vitamin C) **18** with alkyl mesylates **19** using sodium hydrogen carbonates as a base and yields the 3-O-alkyl ethers of $_{L}$-ascorbic acid **20** (Scheme 7). $_{L}$-ascorbic acid (Vitamin C) have antioxidative properties (Kuellmer et al., 1998).The study shows that, at higher temperatures 3-O-alkyl ethers exhibit antioxidative property.

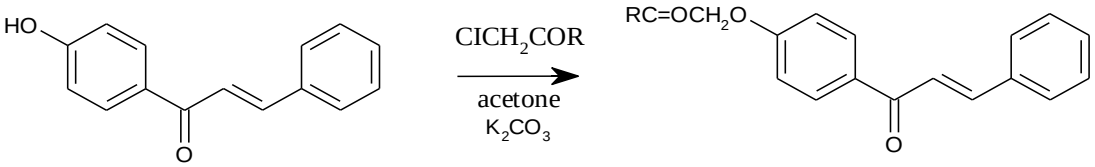


R=C_5H_{11}, C_6H_{13}, C_7H_{15}, C_8H_{17}, C_9H_{19}, $C_{10}H_{21}$, $C_{11}H_{23}$, $C_{12}H_{25}$, $C_{13}H_{27}$, $C_{14}H_{29}$, $C_{15}H_{31}$ and $C_{16}H_{33}$

Scheme 7

In 2002, Choi and Cha synthesized a new photoreactive soluble polyimide and polymethacrylate (PMAC). For this research they introduced chalcone group into the side chain unit of the new photoreactive polymers. Chalcone compound was used because of the highly sensitive properties to the linearly polarized light. In polymetacrylate, the monomer of metacrylate was synthesized using metacryloyl chloride and 4-hydroxychalcone. The soluble polyimide was synthesized through condensation with specific dianhydride and diamine with two trifluoromethyl groups. Choi and Cha anchored the chalcone with ethylene spacer which is 4-(2-hydroxyetoxy)-chalcone to avoid the geometrical hindrance that can cause low yield. Substitution was found to be 80%.

Pyralozine are well-known nitrogen-containing heterocyclic compound that found to posses important bioactivities such as immunosuppressive activities (Lombardino and Ottenes, 1981). For that reason, in 2007 Levai and Jeko prepared 2-pyrazolines compound **21** bearing a carboxylic acid ester or carboximide side chain by treatment of the appropriate chalcone derivatives with hydrazine hydride or phenylhydrazine in hot acetic acid (Scheme 8).



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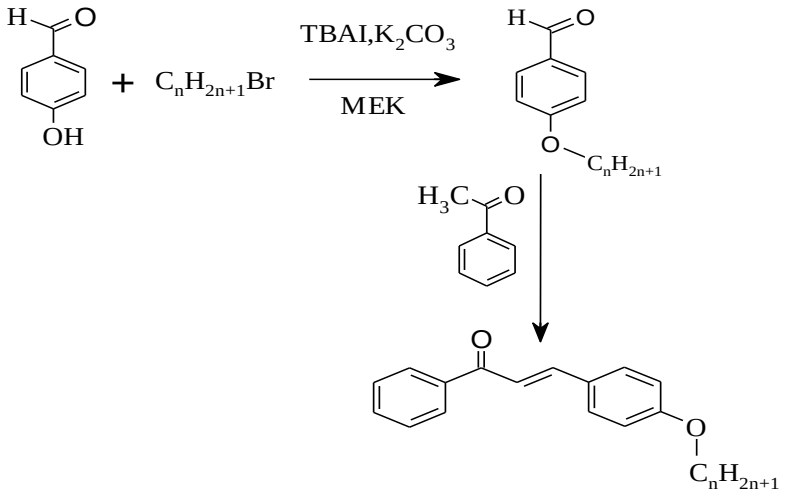
Scheme 8

CHAPTER 3

MATERIAL AND METHODOLOGY

EXPERIMENTAL SECTION

Strategy 1: Etherification Process Followed by Synthesis of Chalcone

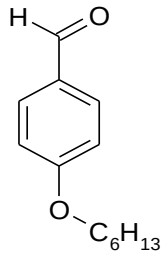


Scheme 9

3.1 General procedure of Etherification Process

A mixture of 4-hydroxybenzaldehyde, 1-bromoalkane (6, 7, 8, 9) , K_2CO_3 and TBAI in methyl ethyl ketone was heated and reflux for 18 hour. The mixture was cooled to room temperature and filtered. DCM and water are used to extract the organic layer (2 x). Dried, filtered, and concentrated under reduced pressure. Pure product was obtained from column chromatography or recystallization.

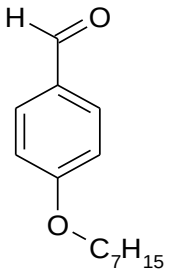
Etherification process of 4-hexyloxybenzaldehyde (22)



22

A mixture of bromohexane (5.05 mL, 36 mmol), 4-hydroxybenzaldehyde (3.66 g, 30.0 mmol), potassium carbonate (4.98 g, 36.0 mmol) and TBAI (1.1 g, 3.0 mmol) in MEK (90 mL) was heated at reflux for 18 hr. The mixture was cooled to room temperature and worked up according to the general procedure to give the title compound **22** (60%) as yellowish oil. R_f 0.7 ethyl acetate: petroleum ether (1:7) IR ν_{max} : 1694 (C=O), 1160 cm^{-1}(C-O), 2933 cm^{-1}(CH stretch), 1602 cm^{-1} (C=C aromatic).

Etherification process of 4-heptyloxybenzaldehyde (23)

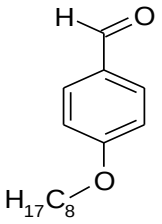


23

A mixture of bromoheptyl (5.05 mL, 36 mmol), 4-hydroxybenzaldehyde (3.66 g, 30.0 mmol), potassium carbonate (4.98 g, 36.0 mmol) and TBAI (1.1 g, 3.0 mmol) in MEK (90 mL) was heated at reflux for 18 hr.

The mixture was cooled to room temperature and worked up according to the general procedure to give the title compound **23** (75%) as yellowish oil. R_f 0.7 ethyl acetate: petroleum ether (1:7). IR ν_{max} : 1694 cm^{-1} (C=O), 1160cm^{-1} (C-O), 2930 cm^{-1} (CH stretch), 1602 cm^{-1} (C=C aromatic).

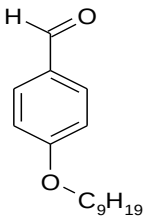
Etherification process of 4-octyloxybenzaldehyde (24)



24

A mixture of bromohexane (5.05 mL, 36 mmol), 4-hydroxybenzaldehyde (3.66 g, 30.0 mmol), potassium carbonate (4.98 g, 36.0 mmol) and TBAI (1.1 g, 3.0 mmol) in MEK (90 mL) was heated at reflux for 18 hr. The mixture was cooled to room temperature and worked up according to the general procedure to give the title compound **24** as yellowish oil.R_f 0.7 ethyl acetate: petroleum ether (1:6). IR ν_{max} : 1694 cm^{-1} (C=O), 1291 cm^{-1} (C-O), 2928 cm^{-1} (CH stretch), 1602 cm^{-1} (C=C aromatic).

Etherification process of 4-nonyloxybenzaldehyde (25)



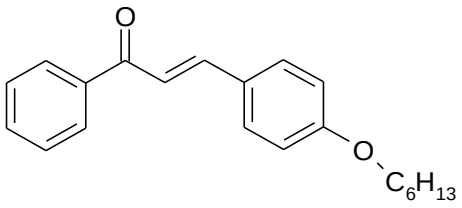
25

A mixture of bromononyl (5.05 mL, 36 mmol), 4-hydroxybenzaldehyde (3.66 g, 30.0 mmol), potassium carbonate (4.98 g, 36.0 mmol) and TBAI (1.1 g, 3.0 mmol) in MEK (90 mL) was heated at reflux for 18 hr. The mixture was cooled to room temperature and worked up according to the general procedure to give the title compound **25** (70%) as yellowish oil. R_f 0.7 ethyl acetate: petroleum ether (1:7). IR ν_{max} : 1695 cm^{-1} (C=O), 1160 cm^{-1} (C-O), 2926 cm^{-1} (CH stretch), 1602 cm^{-1} (C=C aromatic).

3.2 General procedure for synthesis of chalcone derivatives

A mixture of KOH, acetophenone and alkoxybenzaldehyde in EtOH (95 %) was stirred 18 hour. The reaction mixture was then cooled in an ice bath. HCl was added drop by drop until a yellow precipitate formed. The precipitate filtered and washed with distilled water.

Synthesis of 3-(4-Hexyloxy-phenyl)-1-propenone (26)

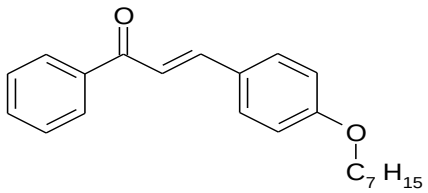


26

Potassium hydroxide (0.56 g, 10 mmol) in ethanol (30 mL 95%) was stirred for 20 minutes and cooled to room temperature over 30 minutes. 4-hexyloxy-benzaldehyde (2.34 mL, 10 mmol) and acetophenone (0.99 mL, 10 mmol) was then added to the solution mixture respectively. The reaction mixture was stirred for 18 hr at room temperature.

The mixture was then cooled in ice bath and 8 M HCI was added drop by drop until yellow precipitates formed and worked up according to the general procedure. The crude was recrystallized in hot ethanol 95 % to give the title compound **26** (48.7%) as a yellowish crystals; m.p 72.6 – 74.6 ^{0}C. R_f 0.7 ethyl acetate: petroleum ether (1: 6). IR ν_{max} : 1652 cm^{-1} (C=C), 3062 cm^{-1} (CH aromatic), 1017 cm^{-1}(C-O), 2942 cm^{-1}(CH stretch);^{1}H NMR ($CDCl_3$, 500 MHz):δ (ppm) 6.8-6.9 (1H in ethylenic –C<u>H</u>=CH-C(=O)-,d), 7.9-8.0 (1H in ethylenic –CH=C<u>H</u>-C(=O)-,d), 7.3-7.7 (9H in aromatic group). ^{13}C NMR δ (ppm): 190.6, 161.3, 144.7, 138.4, 132.4, 130.1, 128.4, 128.3, 127.2, 119.5, 114.8, 68.1, 31.4, 29.1, 29.0, 25.6, 22.5, 14.0

Synthesis of 3-(4-Heptyloxy-phenyl)-1-propenone (27)

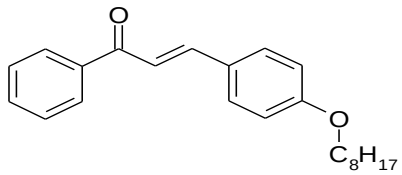


27

Potassium hydroxide (1.12 g, 20 mol) in ethanol (60 mL 95%) was stirred for 20 minutes and cooled to room temperature over 30 minutes. 4-heptyloxy-benzaldehyde (4.4 mL, 20 mmol) and acetophenone (1.99 mL, 20 mmol) was then added to the solution mixture respectively. The reaction mixture was stirred for 18 hr at room temperature. The mixture was then cooled in ice bath and 8 M HCI was added drop by drop until yellow precipitates formed and worked up followed the general procedure.

The crude was recrystallized in hot ethanol 95 % to give the title compound **27** (41 %) as a pale yellow plough solid; m:p 66.7 – 68.6 ^{0}C. R_f 0.74 ethyl acetate: petroleum ether (1 : 6). IR ν_{max} : 1654 cm^{-1} (C=C), 1018 cm^{-1}(C-O), 2926 cm^{-1}(CH stretch), 3066 cm^{-1} (CH aromatic). ^{1}H NMR ($CDCl_3$, 500 MHz):δ (ppm) 6.8-6.9 (1H in ethylenic –C<u>H</u>=CH-C(=O)-,d), 7.5-7.6 (1H in ethylenic –CH=C<u>H</u>-C(=O)-,d), 7.3-7.7 (9H in aromatic group). ^{13}C NMR δ (ppm): 190.6, 161.3, 144.8, 138.5, 132.5, 130.2, 128.5, 128.3, 127.3, 119.5, 114.8, 68.1, 31.7, 29.1, 29.0, 25.9, 22.5, 14.0

Synthesis of 3-(4-octyloxy-phenyl)-1-propenone (28)

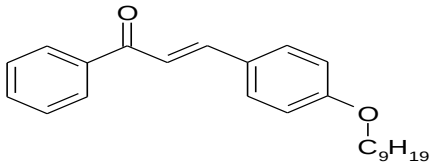


28

Potassium hydroxide (1.12 g, 20 mmol) in ethanol (60 mL 95%) was stirred for 20 minutes and cooled to room temperature over 30 minutes. 4-octyloxy-benzaldehyde (4.68 mL, 20 mmol) and acetophenone (1.99 mL, 20 mmol) was then added to the solution mixture respectively. The reaction mixture was stirred for 18 hr at room temperature. The mixture was then cooled in ice bath and 8 M HCI was added drop by drop and worked up according to the general procedure.The crude was recrystallized in hot ethanol 95 % to give the title compound **28** (57.3 %) as an orange plough solid; m.p 74.8 – 75.5 ^{0}C. R_f 0.78 ethyl acetate: petroleum ether (1:6). IR ν_{max} : 1650 cm^{-1} (C=C), 1015 cm^{-1}(C-O), 2924 cm^{-1}(CH stretch), 3064 cm^{-1} (CH aromatic).

^{1}H NMR ($CDCl_3$, 500 MHz):δ (ppm) 6.8-6.9 (1H in ethylenic –C<u>H</u>=CH-C(=O)-,d), 7.5-7.6 (1H in ethylenic –CH=C<u>H</u>-C(=O)-,d), 7.3-8.0 (9H in aromatic group). ^{13}C NMR δ (ppm): 190.5, 161.3, 144.8, 138.5, 132.5, 130.2, 128.7, 128.5, 128.3, 127.3, 119.5, 114.8, 68.1, 31.7, 29.1, 29.2, 25.9, 22.6, 14.1

Synthesis of 3-(4-nonyloxy-phenyl)-1-propenone (29)

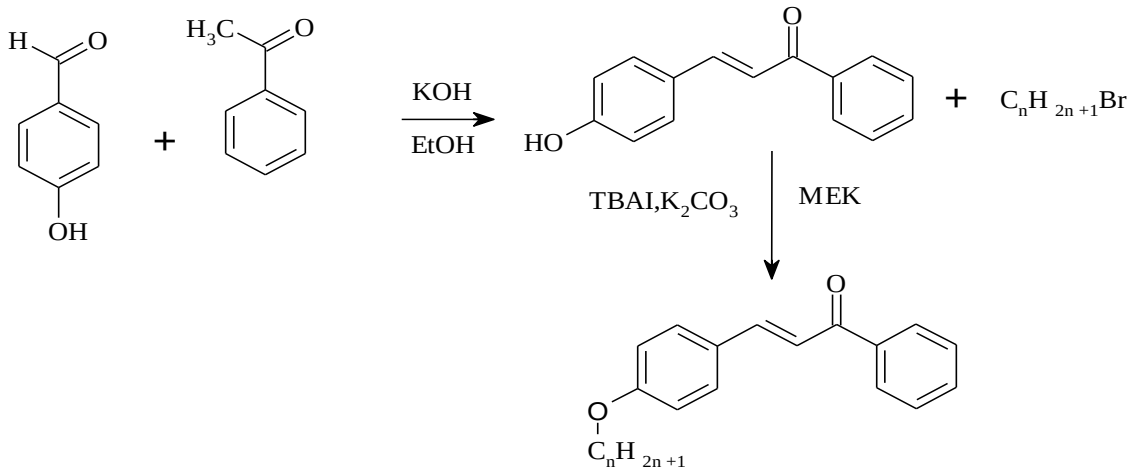


29

Potassium hydroxide (0.26 g, 4.6 mmol) in ethanol (60 mL 95%) was stirred for 20 minutes and cooled to room temperature over 30 minutes. 4-nonyloxy-benzaldehyde (1.61 mL, 4.6 mmol) and acetophenone (0.46 mL, 4.6 mmol) was then added to the solution mixture respectively. The reaction mixture was stirred for 18 hr at room temperature. The mixture was then cooled in ice bath and 8 M HCI was added drop by drop and the worked up according to the general procedure.The crude was recrystallized in hot ethanol 95 % to give the title compound **29** (64.6 %) as a yellow crystal; m.p 82.3 – 83.3 ^{0}C.R_f 0.76 ethyl acetate : petroleum ether (1 : 6)

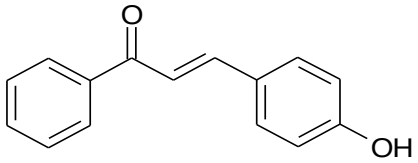
IR ν_{max} : 1650 cm^{-1} (C=C), 1015 cm^{-1}(C-O), 2924 cm^{-1}(CH stretch), 3064 cm^{-1} (CH aromatic). ^{1}H NMR ($CDCl_3$, 500 MHz):δ (ppm) 6.8 (1H in ethylenic –C<u>H</u>=CH-C(=O)-,d), 7.1 (1H in ethylenic –CH=C<u>H</u>-C(=O)-,d), 7.3-8.0 (9H in aromatic group). ^{13}C NMR δ (ppm): 190.5, 161.7, 144.8, 138.5, 132.5, 130.2, 128.7, 128.5, 128.3, 127.3, 119.5, 114.6, 68.1, 31.9, 29.3, 29.1, 26.0, 22.5, 14.1

Strategy 2: Synthesis of chalcone followed by etherification process



n= 6, 7, 8, 9
Scheme 10

3.3 Synthesis of 3-(4-Hydroxy-phenyl) - 1 - propenone (30)



30

Potassium hydroxide (25 g, 100 mmol) in ethanol (300 mL, 95%) was stirred for 30 minutes and the reaction was allowed to cool to room temperature over 30 minutes. 4-hydroxybenzaldehyde (12 g, 100 mmol) and acetophenone (120.15 mL, 100 mmol) was then added to the solution mixture respectively. The reaction mixture was stirred for 18 hr at room temperature.The mixture was cooled in ice bath and 8 M HCl was added drop by drop until a yellow precipitate formed. The mixture was filtered and washed with distilled water.