

Synthesis and Characterization of 2,6-Dihydroxy Substituted Chalcones Using PEG-400 as a Recyclable Solvent

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Abstract:

A novel method for the synthesis of 2,6-dihydroxy substituted chalcones via Claisen-Schmidt is introduced using recyclable PEG-400 as an alternative reaction solvent. The reaction is clean with excellent yield, shorter reaction time and reduces the use of volatile organic compounds (VOCs). The structures of the synthesized compounds were confirmed by IR, mass spectroscopy and elemental analysis.

Keywords: *Chalcone, Claisen-Schmidt condensation, PEG-400, IR, Mass and Elemental spectral analysis*

Introduction:

In recent years, Chalcones have found a wide range of applications in the pharmacological activities such as, potential cytotoxic agents, antiviral, anesthetics, mydriatics, antimicrobial, antimitotic, antitumor, cytotoxicity, and antipyretic properties[1-9] The presence of a reactive α,β -unsaturated ketone function in chalcones is found to be responsible for their antimicrobial activity which may be altered depending on the type and position of substituent aromatic rings. They also act as potential antiulcer, antifungal, anticancer [10] and antimalarial agents [11] Chalcones are a group of compounds with various substitution patterns on the two aromatic rings of 1,3-diphenyl-2-propene-1-one, that are considered as the precursor of flavonoids and isoflavonoids are abundant in edible plants. Chalcones have been prepared by condensing aryl ketones with aromatic aldehydes in presence of suitable condensing agents. They undergo a variety of chemical reactions and are found to be useful in the synthesis of variety of heterocyclic compounds[12] like isoxazoles, quinolinones, thiadiazines, benzofuranones, benzodiazepine, tetrahydro-2-chromens [13] flavones etc., Moreover, these are important intermediates in many addition reactions of nucleophiles due to inductive polarization of carbonyl group at the β -position. These findings explain the significant interest of scientist in this particular group of compounds.

Several strategies for the synthesis of these system, based on the formation of carbon-

carbon bond have been reported. Among them the direct Aldol condensation and Claisen-Schmidt condensation still occupy prominent positions. The main method for the synthesis of chalcones is the classical Claisen-Schmidt condensation in the presence of aqueous alkaline bases,[14] $\text{Ba}(\text{OH})_2$ [15] LiOH , microwave irradiation and ultrasound irradiation [16]. They are also obtained via Suzuki reaction,[17] Wittig reaction, Friedel-Crafts acylation with cinnamoyl chloride, or Photo-Fries rearrangement of phenyl cinnamates. In aldol condensation the preparation of chalcones requires at least two-steps aldol formation and dehydration. Since aldol addition is reversible, mukaiyama or Claisen-Schmidt condensation approach of using enol ether has emerged as an alternative pathway.

The aldol reaction is also performed under acidic medium,[18] using HCl , BF_3 , B_2O_3 , *p*-toluenesulfonic acid etc. Recently various modified methods for the synthesis of chalcones has been reported, such as by using SOCl_2 ,[19] natural phosphate, lithium nitrate,[20] amino grafted zeolites,[21] zinc oxide, water,[22] Na_2CO_3 ,[23], PEG_{400} ,[24] silicasulfuric acid,[25, 26] ZrCl_4 and ionic liquid [27] etc. Jhala et al. synthesized chalcone using basic alumina under micro wave irradiation. However, many of these methods suffered from harsh reaction condition, toxic reagents, strong acidic or basic conditions, prolonged reaction-times, poor yields and low selectivity. Although, several modifications have been made to counter these problems. There is still a need for the development of selective and

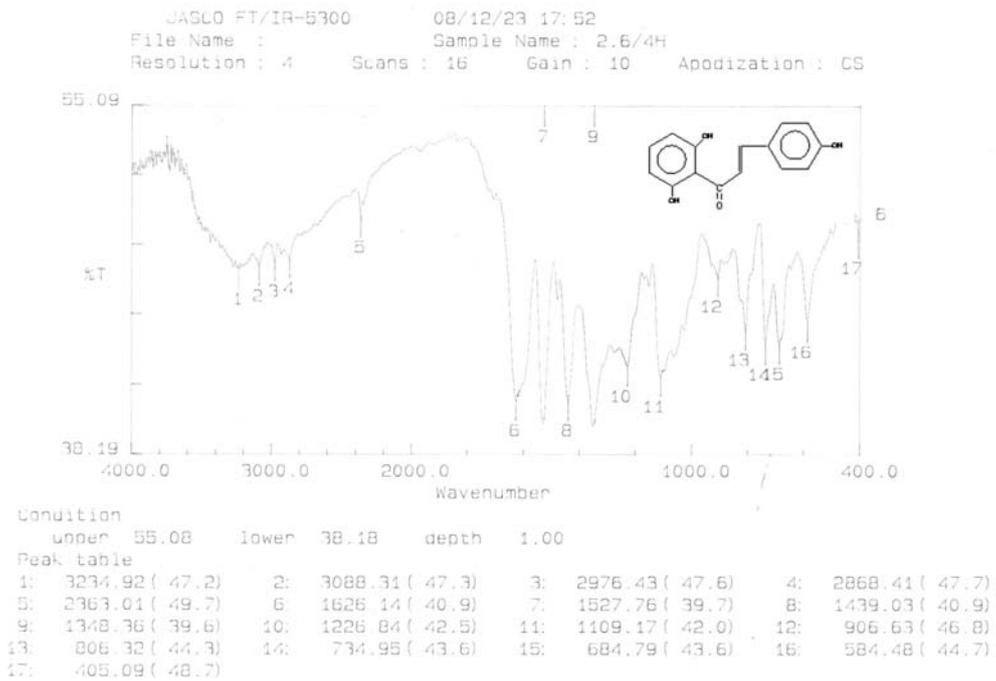


Fig. 1: IR data of 1-(2,6- dihydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one

**LCMS-2010A DATA REPORT
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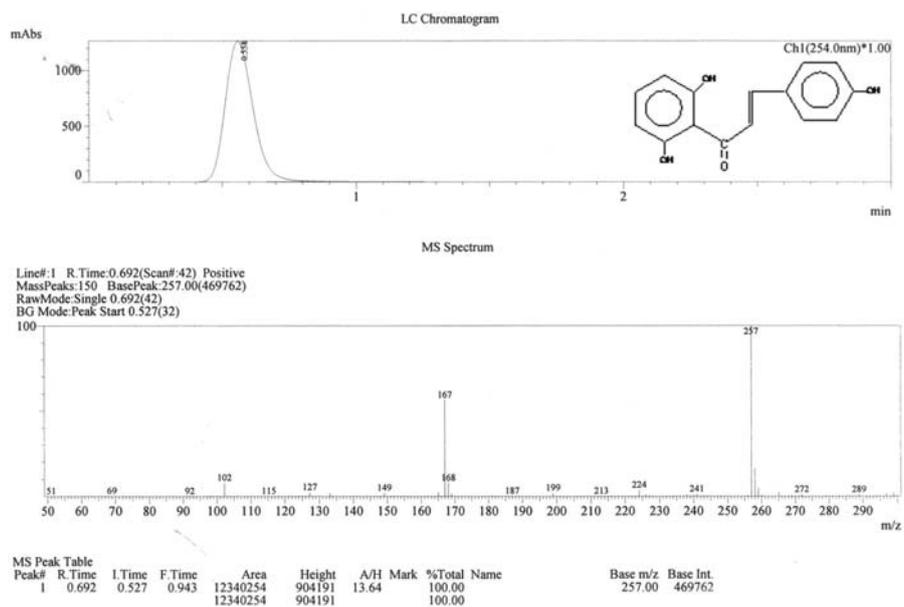
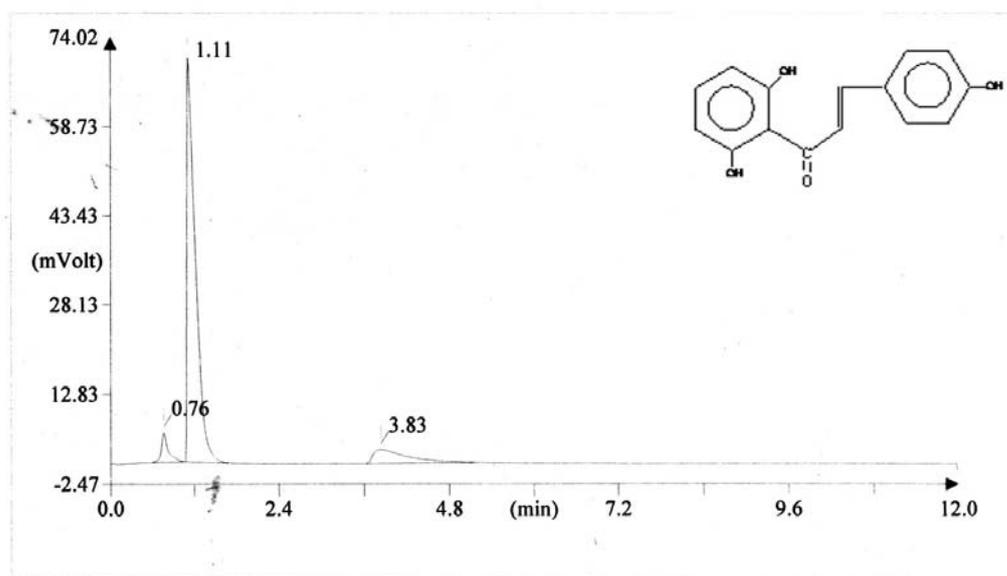


Fig. 2: Mass spectral data of 1-(2,6- dihydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one

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Method filename: I:\Program Files\Thermo Finnigan\Eager 300 for EA1112\DATA\Sys_data_exa
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 Analysis type: UnkNown
 Chromatogram filename: UNK-12112009-3.dat
 Sample weight: 1.278



Element Name	Element %	Ret. Time
Nitrogen	0. 11	0. 76
Carbon	70. 41	1. 11
Hydrogen	4. 68	3. 83

Fig. 3: Elemental analysis data of 1-(2,6- dihydroxyphenyl)-3-(4-hydroxy phenyl)prop-2-en-1-one

better strategies for the synthesis of α , β -unsaturated carbonyl compounds.

However, many of these methods suffered from harsh reaction condition, toxic reagents, strong acidic or basic conditions, prolonged reaction times, poor yields and low selectivity. Although, several modifications had been made to counter these problems. There is still a need for the development of selective and better

strategies for the synthesis of α , β -unsaturated carbonyl compounds.

Herein for the first time we describe a simple and convenient method for the synthesis of chalcones using poly ethylene glycol (PEG) has been found to be an interesting solvent system. In continuation of own work on chalcones as perrecursorsin the synthesis of various heterocycles [28], we have planned to

synthesize a series of novel hetero chalcones by applying the principles of

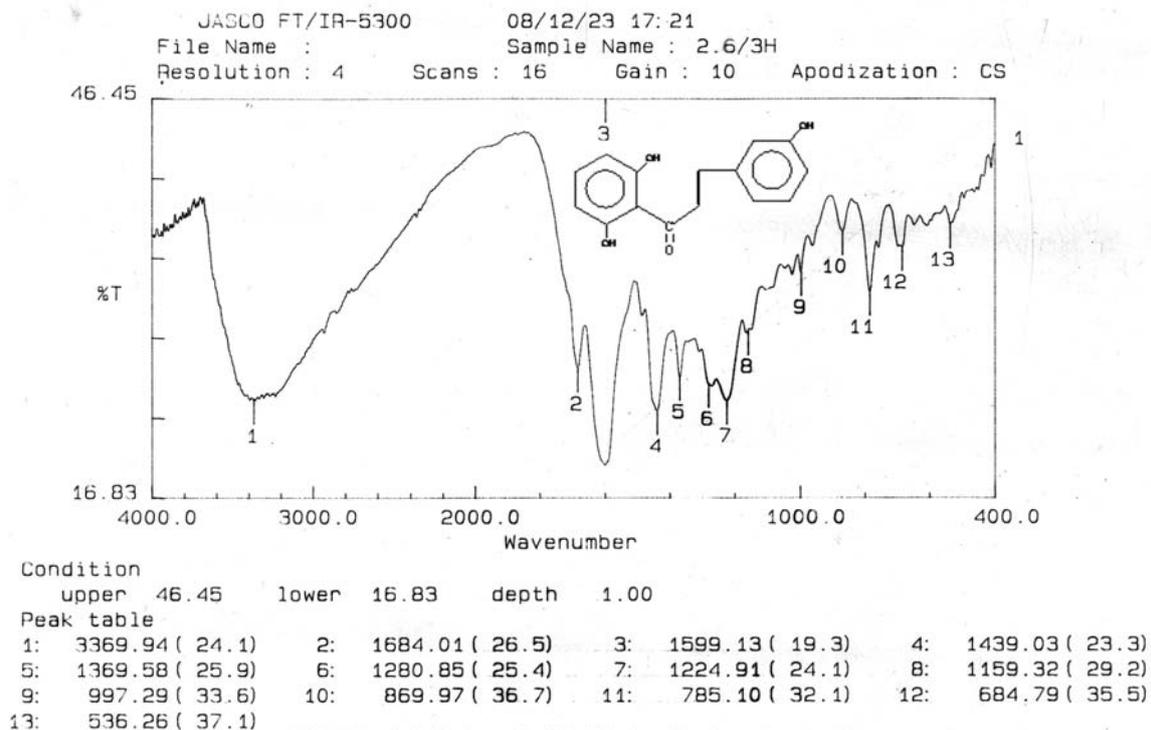


Fig.4: IR data of 1-(2,6- dihydroxyphenyl)-3-(3-hydroxyphenyl)prop-2-en-1-one

**LCMS-2010A DATA REPORT
 SHIMADZU**

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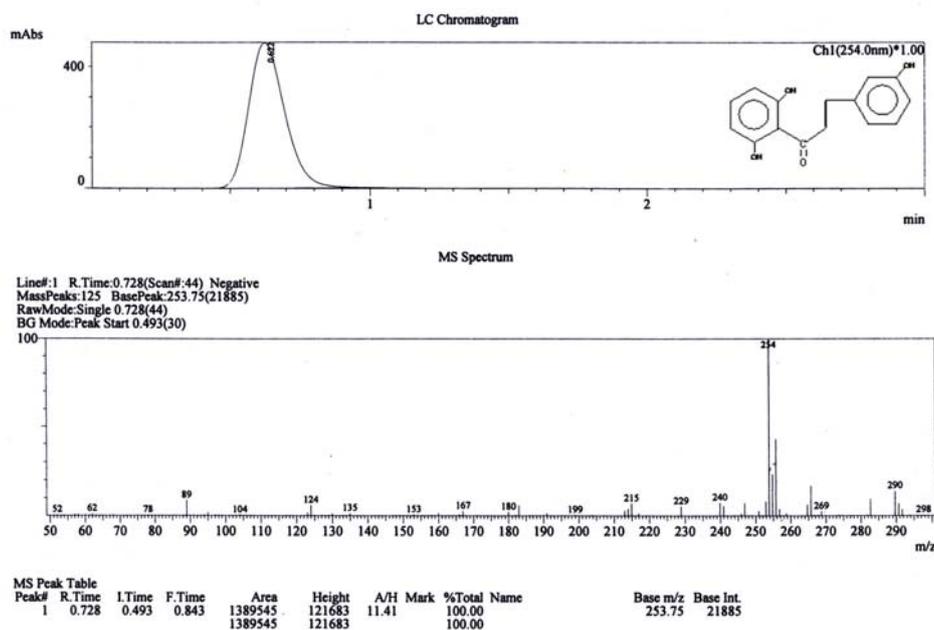
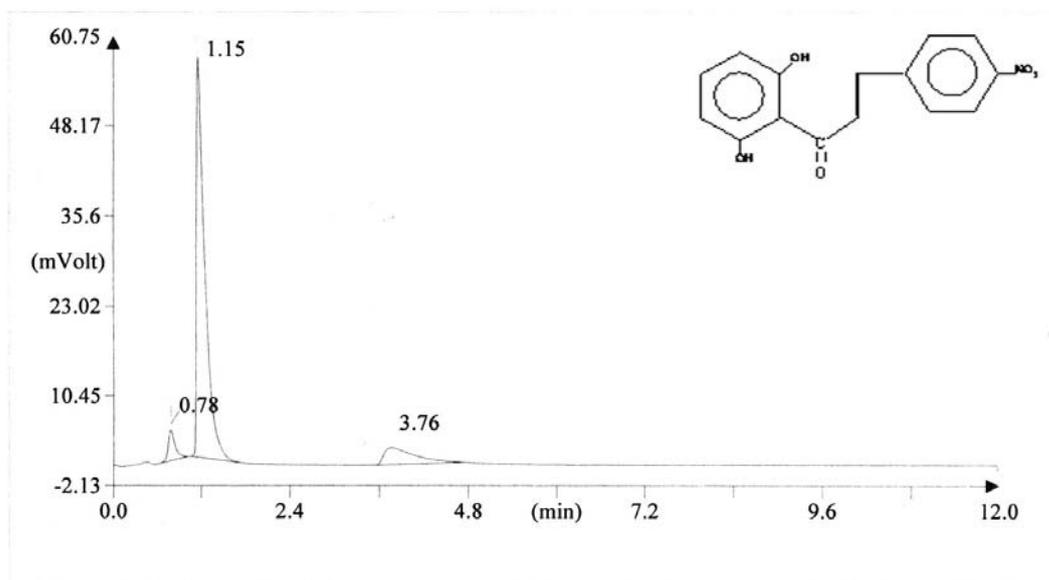


Fig. 5: Mass spectral data of 1-(2,6- dihydroxyphenyl)-3-(3-hydroxyphenyl) prop-2-en-1-one

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 Chromatogram filename: UNK-26102009-12.dat
 Sample weight: .996



Element Name	Element %	Ret. Time
Nitrogen	0.09	0.78
Carbon	70.18	1.15
Hydrogen	4.58	3.76

Fig. 6: Elemental analysis data of 1-(2,6- dihydroxyphenyl)-3-(3-hydroxy phenyl)prop-2-en-1-one

Table.1: Physicochemical characterization data for synthesized compounds

Compound Number	Molecular formula	Molecular weight	Yield (%)	M.P °C	Elemental analysis		
					C	H	N
1	C ₁₅ H ₁₁ ClO ₃	274	71	198	66.54 (66.75)	4.06 (4.04)	-
2	C ₁₅ H ₁₂ O ₄	256	75	140	70.41 (70.37)	4.68 (4.72)	-
3	C ₁₅ H ₁₂ O ₄	256	81	190	70.18 (70.37)	4.58 (4.72)	-
4	C ₁₅ H ₁₁ NO ₅	285	64	192	63.24 (63.21)	4.72 (3.89)	4.96 (4.91)

Table.2: Interpreted IR spectral data of synthesized compounds

Compound number	Compound	IR. Spectral data
1	3-(4-chlorophenyl)-1-(2,6-dihydroxyphenyl) prop-2-en-1-one	IR (KBr) ν cm^{-1} , (-OH) 3212 cm^{-1} , (C=O) 1682 cm^{-1} , (C=C) 1591 cm^{-1}
2	1-(2,6-dihydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one	IR (KBr) ν cm^{-1} , (-OH) 3234 cm^{-1} , (C=O) 1626 cm^{-1} , (C=C) 1527 cm^{-1}
3	1-(2,6-dihydroxyphenyl)-3-(3-hydroxyphenyl) prop-2-en-1-one	IR (KBr) ν cm^{-1} , (-OH) 3369 cm^{-1} , (C=O) 1684 cm^{-1} , (C=C) 1599 cm^{-1}
4	1-(2,6-dihydroxyphenyl)-3-(4-nitrophenyl) prop-2-en-1-one	IR (KBr) ν cm^{-1} , (-OH) 3200 cm^{-1} , (C=O) 1672 cm^{-1} , (C=C) 1591 cm^{-1}

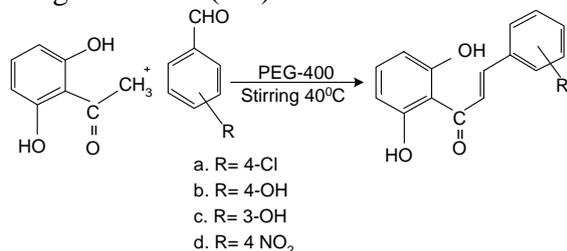
Table.3: Mass spectral data of synthesized compounds

Compound Number	Compound data	Molecular weight	Mass spectral
1	3-(4-chlorophenyl)-1-(2,6-dihydroxyphenyl) prop-2-en-1-one	274	274 M^{+2}
2	1-(2,6-dihydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one	256	$256 \text{ M}^+\text{H}$
3	1-(2,6-dihydroxyphenyl)-3-(3-hydroxyphenyl) prop-2-en-1-one	256	$256 \text{ M}^+\text{H}$
4	1-(2,6-dihydroxyphenyl)-3-(4-nitrophenyl) prop-2-en-1-one	285	285 M^+

green chemistry, using PEG400 as an alternative reaction medium [29]. PEG is an environmentally benign reaction solvent, is it non-toxic, inexpensive, potentially recyclable and water soluble, which facilitates its removal from the reaction product.

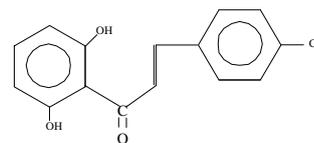
Materials and Methods:

All the products were synthesized and characterized by their spectral analysis. Chemicals, 2,6-dihydroxy acetophenone, 2-chloro benzaldehyde, 4-chloro benzaldehyde, 3-nitrobenzaldehyde were purchased from S.D. fine Chemicals (India). Melting points were uncorrected and determined in an open capillary tube. IR spectra were recorded in KBr on a JASCO FT/IR-5300 The mass spectra were recorded on LCMS-2010 DATA REPORT SHIMADZU Spectrometer Elemental analysis was carried out on a FLASH EA 1112 SERIES CHN REPORT THERMO FINNIGAN. Chalcones were synthesized by Claisen-Schmidt condensation using PEG-400 as reaction. Solvent. The chemicals and solvent used were of laboratory grade and were purified completion of the reaction was monitored by thin layer chromatography on precoated sheets of silica gel-G (Merck, Germany) using iodine vapour for detection. The synthetic pathway is presented in Scheme 1 and physicochemical data and spectral data for the synthesized compounds are given Table (1-3).



Scheme 1: Synthetic diagram of 2,6-dihydroxy substituted chalcones

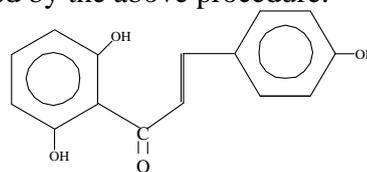
1) Synthesis of 3-(4-chlorophenyl)-1-(2,6-dihydroxyphenyl) prop-2-en-1-one



An equimolar mixture of 2,6-dihydroxy acetophenone(2.2), aromatic aldehydes(2.2) and KOH (5ml) was stirred in PEG-400 (10ml) at 40°C for 1 hour after the completion of the reaction (monitored by TLC), the crude mixture was worked up in ice-cold water (100 ml). The product which separated out was filtered. The filtrate was evaporated to remove water leaving PEG behind. The same PEG was utilized to synthesize further chalcone.

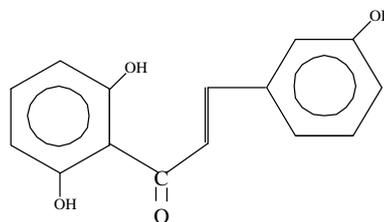
2) Synthesis of 1-(2,6-dihydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one

Reaction with 2,6-dihydroxy acetophenone (2 gm) and 4-hydroxy benzaldehyde (2.1gm); 1-(2,6-dihydroxyphenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one was obtained by the above procedure.



3) Synthesis of 1-(2, 6-dihydroxyphenyl)-3-(3-hydroxyphenyl) prop-2-en-1-one

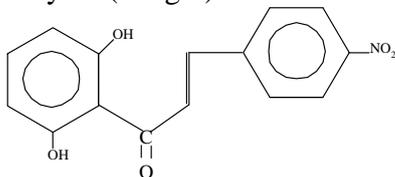
A mixture of 2, 6-dihydroxy acetophenone (2.2 gm) in PEG-400 (10 ml) and 3-hydroxy benzaldehyde (2.1 gm); 1-(2,6-dihydroxyphenyl)-3-(3-hydroxyphenyl) prop-2-en-1-one was obtained by the above procedure.



4) Synthesis of 1-(2, 6-dihydroxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one

1-(2,6-dihydroxyphenyl)-3-(4-nitrophenyl) prop-2 en-1-one was obtained by the above described procedure except that starting

material used was 2,6-dihydroxy acetophenone (2.0) in ethanol (10 ml) 4 nitro benzaldehyde. (2.1 gm).



Results and Discussions:

The Claisen-Schmidt condensation [30] is an important C-C bond formation for the synthesis of 1,3-diaryl-2-propen-1-ones (chalcones). It is generally carried out of the use of strong bases such as Na OH or KOH in polar solvents (MeOH or DMF). The aim of the present study was to develop an efficient protocol using PEG-400 as a recyclable reaction solvent to obtain 1,3-diaryl-2-propen-1-ones with good to excellent yields in a short span of time without formation of any side product. Synthesis of chalcone is a single step method. The synthesized chalcone derivatives were undergone physicochemical characterization and the obtained results are given in Table.2. The yields of the synthesized compounds were found to be significant.

The structure of the synthesized compounds was confirmed by IR, Mass and elemental analysis. Elemental analysis showed that the percentage of the nitrogen, hydrogen and carbon was found experimentally is equivalent to the calculated values in all compounds.

All the compounds give the characteristic IR peak that proved that the presence of particular functional group (Table 2) and mass spectroscopy helps to find the molecular weight of the synthesized compounds (Table 3). The Chalcone derivatives showed that the molecular ion peak that equivalent to the molecular weight of proposed compound. Hence m/z value confirms the molecular weight of the respective synthesized compound.

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