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Non-genotoxic and Eco-friendly Synthesis of Chalcones Using Alum (KAI $SO_4)_2.12H_2O$) as an Efficient and Novel Catalyst

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ABSTRACT

We report a new environmentally-benign, convenient and facile methodology for the synthesis of non-genotoxic Chalcones using Alum (KAI $(SO_4)_2.12H_2O$) as catalyst. The reaction of 2-hydroxy acetophenone with aldehydes in aqueous ethanol at ambient temperature has been studied. The reaction has yielded chalcones in one step. Furthermore, a series of compounds were synthesized and characterized by melting point, Electron Ionization-Mass Spectrometry (EI-MS), Nuclear Magnetic Resonance (NMR) and Infra-Red (IR) tools. The formation of desired product was confirmed by comparing them with reference compounds. Utilization of aqueous medium, easy reaction conditions, isolation and purification makes this manipulation very interesting from an environmental and economic perspective. Synthesized chalcones are non-genotoxic compounds as there is no functional group those are known as a genotoxic as (1) Aromatic compounds such as N-hydroxyaryls, N-acelated aminoaryls, Az-aryl-N-oxides and amino aryls, (2) Alkyl and aryl groups: N-methylols, N-antirasoamines, carbamates, nitro compounds, (3) Heteroaromatic groups such as Michel reactive acceptors, alkyl ester of phosphonates, sulphonates, halo-alkenes, halo-alkanes.

Keywords: Chalcones, Alum, Aldehyde, Acetophenone

INTRODUCTION

Chalcones constitute an important group of natural products. Pharmacological studies of various scaffolds bearing chalcones possess an array of biological activities such as antibacterial, anti-invasive an antifeedant derivatives. The Claisen-Schmidt condensation is basic reaction for the synthesis of chalcones in which aliphatic or aromatic ketones condense with an aldehyde in presence of soluble alkaline hydroxides or Sodium Ethoxide (NaOEt).

Other than the soluble bases various heterogeneous solid bases are also employed to obtain chalcones. These includes alumina, Barium Hydroxide ($Ba(OH)_2$), hydrotalcites, Magnesium Oxide (MgO) and calcined Sodium nitrate ($NaNO_3$)/natural phosphate. The acid catalyzed methodologies include the use of Aluminium Chloride ($AlCl_3$), Boron Trifluoride (BF_3), dry HCl, Titanium Tetrachloride ($TiCl_4$), Zirconium Hydride Dimer (Cp_2ZrH_2)/Nickel(II) Chloride ($NiCl_2$), zeolites and Ruthenium(III) Chloride ($RuCl_3$). Very recently chalcones synthesis has been accomplished by the use Lithium Hydroxide Monohydrate ($LiOH{\cdot}H_2O$) catalyst and by employing Suzuki coupling reaction [1-4].

Chalcones are another class of compounds which are considered as the precursors of flavonoid and isoflavonoid family and have wide distribution in fruits, vegetables, spices, tea and soya based foodstuff. Chalcones have been subject of great interest for their interesting and variable pharmacological activities [5]. Chalcones or 1,3-diaryl-2-propen-1-ones chemically they consist of open-chain flavonoids in which the two aromatic rings are joined by a 3 carbon α, β-unsaturated carbonyl system. The radical quenching property of the phenolic groups in polyhydroxylated chalcones makes them drugs or food preservatives and rapidly gaining attention towards themselves [6]. Chalcones have been reported to possess many useful properties, including anti-inflammatory, antimicrobial, antifungal, antioxidant, cytotoxic, antitumor and anticancer activities. All these are well reported in reviews [7,8].

A number of chalcones derivatives have also been found to inhibit several enzymes in cellular systems including xanthine oxidase [9], aldose reductase [10], epoxide hydrolase [11], protein tyrosine kinase [12,13] and quinine reductase [14]. Alum ($KAI(SO_4)_2{\cdot}12H_2O$) is an acid with extremely wide applications such as in the synthesis of 14*H*-dibenzo xanthenes [15] and coumarins [16]. However, there are no examples for the use of alum as a catalyst in the preparation of chalcones. Alum has been used at least since Roman times for purification of drinking water and industrial process water [17].

The mission of International Council for Harmonisation (ICH) of technical requirements for pharmaceuticals for human use is to achieve greater Harmonisation Worldwide to ensure that safe, effective and high quality medicines are developed.

Less toxic solvents (Class 3) should be used where practical. Solvents with low toxic potential to man, no health-based exposure limit are needed. Alum has been used as a novel catalyst for synthesis of Schiff Base [18].

Impurities are unwanted chemicals, have no therapeutic value and are potentially harmful. Those impurities that are DNA/RNA reactive are called genotoxic impurities. Genotoxicity is the ability of a compound that can cause destructive effect on a cell's genetic material (DNA, RNA) affecting its integrity. Genotoxic compounds may induce genetic mutations and/or chromosomal rearrangements and can therefore act as carcinogenic compounds. They can interact with DNA and/or its associated cellular components (e.g. the spindle apparatus) or enzymes (e.g. topoisomerases). There are 3 categories of genotoxic impurities: Carcinogenicity i.e., (1) Cancer causing ability, (2) Mutagenicity i.e., mutation causing ability, (3) Teratogenicity i.e., birth defect-causing ability.

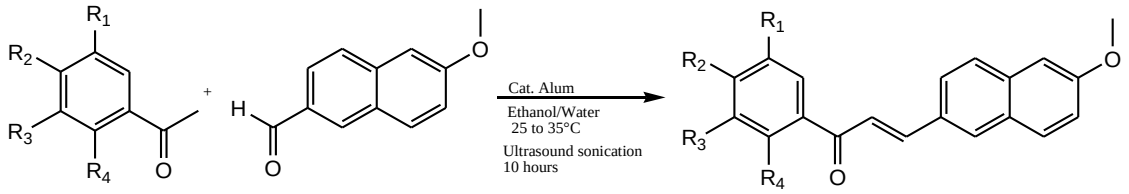
MATERIALS AND METHODS

Materials

All chemicals were obtained from commercial suppliers and were used without purification.

Methods

As a continuation of our research devoted to the development of green organic chemistry by performing organic transformations using ethanol as the reaction medium. We have developed an efficient methodology for the synthesis of substituted chalcones by condensation of 6-methoxy naphthalene 2-carbaldehyde with 2-hydroxy acetophenone using alum (100 mol%) as an inexpensive catalyst in ethanol, which makes use of milder reaction conditions over the reported procedure as depicted in Scheme 1:



Scheme 1: synthesis of substituted chalcones by condensation of 6-methoxy naphthalene 2-carbaldehyde with 2-hydroxy acetophenone using alum

RESULTS AND DISCUSSION

The methodology developed is simple with good to excellent yields of products. We first compared the catalyst effect on different solvents for the synthesis of chalcones as summarized in Table 1. Regulatory assessments of these solvents with low toxic potential to man; no health-based exposure limit is needed [18].

We kept the catalyst constant and used different solvents: Chloroform ($CHCl_3$), Dichloromethane (CH_2Cl_2), Tetrahydrofuran (THF), Dimethylformamide (DMF), methanol, Dimethyl Sulfoxide (DMSO), Acetonitrile (ACN) and dioxane, all afforded a very low yield of product (Table 1). Only ethanol showed good yield. Varying the amount of catalyst 25, 50 and 75 mol% showed unreacted starting material. 100 mol% showed complete reaction with good yield in ethanol (Table 1). These results suggest that ethanol is the best solvent for the synthesis of chalcones.

Alum is soluble in water, hence reaction also tried using water as a solvent, but reaction showed presence of starting material. Hence rule out use of water as a solvent for the reaction. An equimolar mixture of 6-methoxy naphthalene 2-carbaldehyde (1.0 g, 0.005 mol%) and 2-hydroxy acetophenone (0.53 ml, 0.005 mol%) in 10 ml ethanol containing alum (100 mol%) was sonicated at ultrasound irradiation for 10 h. After completion of reaction (checked by TLC), then pH of reaction mass adjusted to 2-3 by using 2 N HCl, Yellow solid obtained. Stirred for 30 min, filtered the solid which was washed with petroleum ether followed by crystallization using ethanol (89%).

Table 1: Solvent effects on the reaction of 6-methoxy naphthalene 2-carbaldehyde and 2-hydroxy acetophenone in the presence of alum ($KAI(SO_4)_2.12H_2O$)

Entry	Solvent	Catalyst mol%	Time (h)	Yield (%)
1	$CHCl_3$	100	16	38
2	CH_2Cl_2	100	16	40
3	THF	100	16	48
4	DMF	100	16	43
5	MeOH	100	4	48
6	ACN	100	16	53
7	Dioxane	100	8	38
8	DMSO	100	16	50
9	EtOH	100	2	89

Standard conditions: 2-Hydroxy acetophenone, 6-methoxy naphthalene 2-carbaldehyde (1 mol), alum catalyst (100 mol%), solvent ethanol, at room temperature. Isolated yield based on starting 6-methoxy naphthalene 2-carbaldehyde.

Reactions were monitored by TLC (silica, Ethyl acetate: Hexane (80:20)). ^{1}H-NMR spectra were recorded on a 400MHzVarian-Mercury Plus spectrometer and are reported as parts per million (ppm) downfield from tetra methylsilane as internal standard. Abbreviations are used as singlet (s), doublet (d), triplet (t) and multiplet (m). Mass spectra were taken with a Waters Micromass Quattro-II mass spectrometer. Physical Data of the compounds (a-i) are provided in the Table 2.

Table 2: Physical data of the compounds (a-i)

Compound number	R	R_2	R_3	R_4	Yield (%)	Melting point (°C) (Reported)
a	H	H	H	H	89	157(156)
b	Cl	H	Cl	H	70	220(220)
c	H	H	Cl	H	69	194(192)
d	Cl	H	H	H	79	166(165)
e	H	H	Br	H	72	188(185)
f	C	H	CH3	H	70	148(149)
g	CH3	H	H	H	60	156(156)
h	H	H	CH3	H	68	134(133)
i	H	CH3	Cl	H	65	188(191)

Representative spectroscopic data for compound

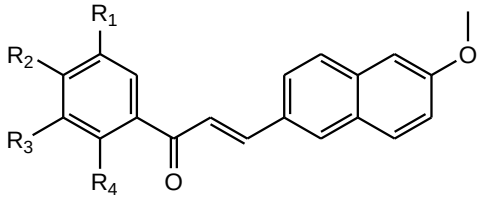
a: (E)-4-methoxy-N-((2-methoxynaphthalen-7-yl)methylene)benzeneamine

Yellow solid; Melting point: 168-172°C. δ=H (DMSO-d6, 400 MHz) 10.41 (s, 1H), 8.24 (s, 1H), 8.12-8.04 (m, 3H), 8.00-7.96 (m, 1H), 7.89-7.79 (3H), 7.38(s, 1H), 7.22 (d, 1H), J=8.8 Hz, 6.92 (s, 1H, J=8.0 Hz), 303.2 $(M^+H)^+$.

Genotoxic information

The synthesis of drug substances involves the use of reactive chemicals, reagents, solvents, catalysts and other processing aids. As a result of chemical synthesis or subsequent degradation, impurities reside in all drug substances and associated drug products. US Pharmacopeia [2] and European Pharmacopeia [3] set the guideline for genotoxic impurities. ICH guideline [4] M7 for genotoxic impurities. Based on these guideline and literature reports about genotoxic impurities categories in three different types which are depends on functional group and chain present in the material/impurities. There are some functional group those are known as a genotoxic[1]: (1) Aromatic compounds such as N-hydroxyaryls, N-acelated aminoaryls, Az-aryl-N-oxides and amino aryls, (2) Alkyl and aryl groups: N-methylols, N-antirasoamines, carbamates, nitro compounds, (3) Heteroaromatic groups such as Michel reactive acceptors, alkyl ester of phosphonates, sulphonates, halo-alkenes, halo-alkanes.

Our synthesized compounds are chalcones family and as per structure and literature search these compounds are non-genotoxic which is major advantage for potential key starting material for synthesis of many drugs such as anticancer, antipsychotic, anti-infantry, antidepressant, antifungal and so on.



R_1, R_2, R_3, R_4=H, Cl, Br, CH_3

Hence our non-genotoxic, eco-friendly and atom efficiency synthesized chalcones are biologically active potential group of many natural products and pharmaceuticals such as anticancer, antipsychotic, anti-infantry, anti-depressant drug products. Our synthesis method is well capable for synthesis of sterically hindered chalcones also.

CONCLUSION

In conclusion, we have developed a new, facile and efficient methodology for the synthesis of (E)-3-(2-methoxynaphthalen-6-yl)-1-phenylprop-2-en-1-one in Ethanol: Water at room temperature within 10 h. using alum as a mild catalyst. The present protocol has several advantages: eco-friendly, mild reaction conditions (at room temperature), shorter reaction time, operational and experimental simplicity. We believed that, Alum promoted methodology will be a valuable addition to the existing processes in the field of (E)-3-(2-methoxynaphthalen-6-yl)-1-phenylprop-2-en-1-one ddifferent reaction conditions (Table 3).

Table 3: (E)-3-(2-methoxynaphthalen-6-yl)-1-phenylprop-2-en-1-one ddifferent reaction conditions

Entry	Solvents	Method/Condition*	Time	Observations
1	Water	A/B	24 h	No Reaction
2	Methanol	A/B	24 h	20-30% product formation
3	Aqueous methanol	A/B	24 h	30% product formation
4	Acetonitrile	A/B	24 h	5-10% product formation
5	Ethanol	A/B	24 h	50-55% product formation
6	Aqueous ethanol	A	10 h	Product formed 60-89%

A: Reaction at room temperature. B: Reaction at reflux temperature. *All reaction carried out by using 100 mol% of alum

Alum [KAI $(SO_4)_2.12H_2O$] as a catalyst provides an efficient methodology for the synthesis of different substituted chalcones from various 2-hydroxy acetophenones with 6-methoxy naphthalene 2-carbaldehyde. The remarkable advantages offered by this method are the use of a stable and inexpensive catalyst, a simple procedure, mild conditions, good to excellent yield of products and use of less toxic solvents ethanol for the reaction. Synthesized derivatives of chalcones are also non-genotoxic.

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