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An efficient synthesis and applications of chalcones in organic synthesis

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ABSTRACT

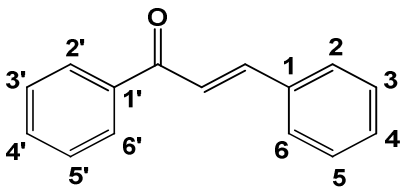
Chalcones are α,β-unsaturated ketones containing the reactive ketoethylenic group CO-CH=CH. The chemistry of chalcones has generated intensive scientific studies throughout the world. Especial interest has been focused on the synthesis and biodynamic activities of chalcones. The name "Chalcones" was given by Kostanecki and Tambor. These compounds are also known as benzalacetophenone or benzylidene acetophenone. In chalcones, two aromatic rings are linked by an aliphatic three carbon chain. Chalcones bear very good synthon framework so that variety of novel heterocycles with good pharmaceutical profile can be designed.

Keywords: α, ß-Unsaturated ketones, Novel heterocycles, Pharmaceutical profile.

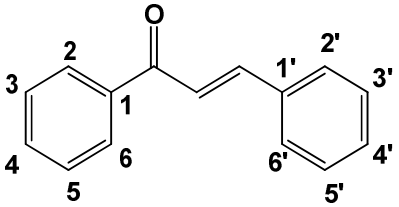
1. INTRODUCTION

1.1. Nomenclatrure of chalcones

Different methods of nomenclatures for chalcone were suggested at different times. The pattern (a) has been adopted by "chemical abstracts" published by American chemical society. The British chemical abstract and journal of chemical society have followed pattern (b) (Fig-1).



(a)



(b)

Figure -1: Nomenclatrure of chalcones

1.2. Biological aspects of chalcones

Chalcones are well known intermediates for synthesizing various heterocyclic compounds and have been reported to exhibit a variety of biological activities [1,2]. They have been reported to possess anti-bacterial [3], anti-platelet [4], antioxidant [5], anti-tubercular [6], anti-ulcerative [7], anti-malarial [8], anti-cancer [9], anti-viral [10], anti-hyperglycemic [11], anti-inflammatory [12] and cytotoxic activity [13]. The presence of reactive chalcone is found to be responsible for their anti-microbial activity which may be altered depending on the type and position of substituent on the aromatic rings.

1.3. Synthetic aspects of chalcones

Different methods are reported in the literature for the preparation of chalcones. The chalcones are versatile reactive intermediates which are used to synthesize several heterocyclic ring systems like five-membered (*e.g.* pyrroles, pyrazoles, imidazoles, isoxazoles, oxazoles, thiazoles, *etc.*), six-membered (*e.g.* pyridines, pyrimidines, triazines, *etc.*), seven-membered (*e.g.* benzodiazepines, benzoxazepines, benzothiazepines, *etc.*) having different heterocycles.

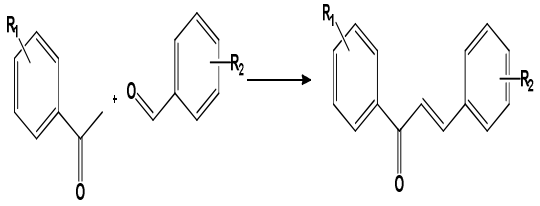
1.4. Conventional methods

1.4.1. Synthesis of *E*-chalcones

1.4.1.1. Claisen-schmidt condensation

The Claisen-Schmidt condensation between acetophenone (1.01) and benzaldehydes (1.02) is a valuable C-C bond forming reaction which allows α,β-unsaturated ketones called

chalcones (1.03) to be obtained. Traditionally, the Claisen-Schmidt condensation [14] is carried out at 50°C using 10-60% of alkali hydroxide or sodium ethoxide over a period of 12-15 hrs (Scheme 1).



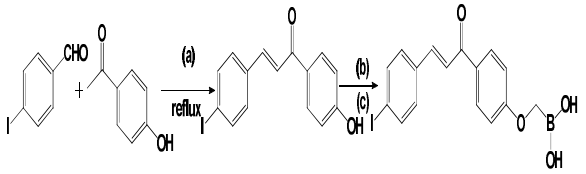
1.01 1.02 1.03

Scheme-1: Claisen-Schmidt condensation

Since aldol condensation is reversible, Claisen-Schmidt condensation [15] approach using enol ether has been emerged as an alternative pathway for this reaction. Claisen-Schmidt condensation of cycloalkanones is not straight forward as these reactions proceed beyond monocondensation. In addition, many of these methods require harsh reaction conditions, expensive and toxic reagents, poor yield and low selectivity. Therefore, several modifications have been made to overcome these problems. There is still a need for the development of selective and better strategies for the one-step generation of α,β-unsaturated carbonyl compounds. It is widely accepted that there is a need to develop clean and economic process, where the use of non-toxic substances and the generation of waste can be avoided. The replacement of liquid by solid base catalysts for the production of fine chemicals not only allows easy separation and recycling of the catalysts from the reaction mixture but also for many bimolecular reactions heterogeneous catalysts give better selectivity than homogeneous catalysts.

Compound 1.07 was prepared by treating compound 1.06 with pinacol (bromomethyl)boronate in the presence of sodium hydride in DMSO and further deprotection in alkaline condition. Compound 1.06 was obtained from 1.04 and 1.05 as shown in the Scheme- 2.

(***Reaction conditions:*** (a) KOH, MeOH (b) NaH, Pinacol (bromoethyl)boronate, THF (c) NaOH, H_2O)

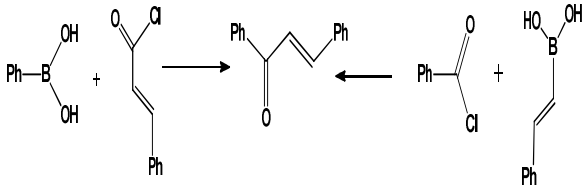


1.04 1.05 1.06 1.07

Scheme- 2

1.4.1.2. Suzuki reaction

A general method for the synthesis of chalcones based on Suzuki reaction between phenyl boronic acid (1.08) and cinnamyl chloride (1.09) or between benzoyl chloride (1.11) and phenyl vinyl boronic acid (1.12) is described in the Scheme-1.3. [16]

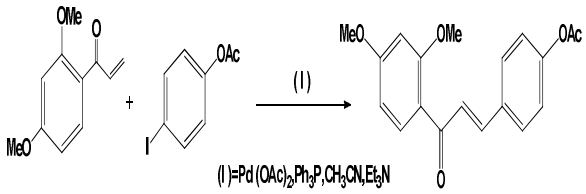


1.08 1.09 1.10 1.11 1.12

Scheme- 3: Suzuki reaction

1.4.1.3. Heck reaction

Coupling of an aryl vinyl ketone (1.13) with an aryl iodide (1.14) in heck reaction condition also resulted chalcones (1.15) and other flavonoids (Scheme - 4). [17]



1.13 1.14 1.15

Scheme – 4: Heck reaction

1.4.1.4. Chalcones from cinnamic acid and its derivatives

Cinnamic acid and phenol [18], cinnamic anhydride [19], cinnamoyl chloride and benzene [20], cinnamoyl chloride and phenol [21] have been used for the synthesis of chalcones and their analogues**.**

1.4.1.5. Chalcones from *o*-iodophenyl acetate and palladium

A convenient palladium catalyzed procedure for the synthesis of *o*-hydroxychalcones, flavanone, and benzo[b]furanes has been described where *o*-iodophenyl acetates were used as a common precursor [22].

1.4.1.6. Chalcones from schiff bases

In presence of acid, arylaminoketones derived from Schiff bases undergo hydramine cleavage to yield primary aromatic amine and chalcones [23].

1.4.1.7. Chalcones from enamines

The synthesis of chalcones has also been affected by the interaction of benzaldehyde with *N*-α-styryl morpholine [24].

1.4.1.8. Chalcones from organometallic compounds

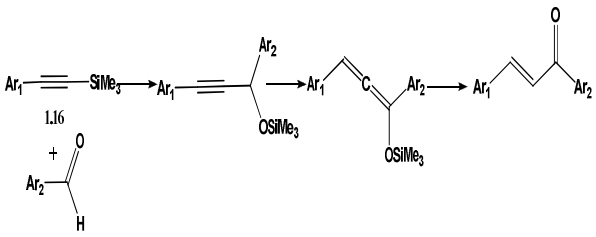
Chalcones have also been synthesized by acetylinic Grignard reagents, cadmium derivatives and cinnamyl chloride in ether, phenyl magnesium bromide and cinnamonitrile in presence of ammonium chloride and methylmagnesium iodide with benzaldehyde [25].

1.4.1.9. Chalcones from critical water

Recently, Zhu *et.al*. has carried out Claisen-Schmidt condensation reaction of aromatic aldehyde and ketone in critical water [26].

1.4.2.1. Synthesis of *Z*-chalcones

Generally, Z-chalcones have great synthetic applications and are synthesized more easily than their *E*-isomers. There have been a few reports [27] concerning to the synthesis of *Z*-isomer of chalcones. Moreover, the general synthetic methods for the *Z*-chalcone is only the photoisomerization of the corresponding *E*-isomer and it takes time to produce the *Z*-chalcones [28]. Recently, various *Z*-chalcone derivatives were easily synthesized in a stereoselective manner from 1,3-diaryl-2-propynyl silyl ether (1.17) which were obtained by the reaction of silyl acetylenes (1.16) with aldehyde catalyzed by a chiral ammonium fluoride. Compound 1.089 on catalytic isomerization by potassiun t-butoxide results the corresponding siloxy allene (1.18). Acid treatment of 1.18 produces in one-pot reaction of the Z-chalcones derivatives (1.19) (Scheme- 5) [29].



1.17 1.18 1.19

Scheme - 5: Synthesis of *Z*-chalcones.

1.5. Non-conventional methods

During the last few decades, chemical application of microwave and ultrasound irradiation has received a lot of attention and widespread research is going on in these areas. Significant enhancement of selectivity, rate of reactions, and yield in synthesis of chlacones has been achieved by means of microwave and ultrasound irradiation.

1.5.1. Microwave irradiated synthesis of chalcones

The following heterogenous catalysts have been used for the synthesis of chalcones and their analogous under microwave irradiation:

- Potassium carbonate
- Barium hydroxide
- *p*-Toluenesulphonic acid [30]
- KF-Al_2O_3 [31]
- Zirconium tetrachloride [32]
- Piperidine
- Aqueous alkali

1.5.2. Ultrasound irradiated synthesis of chalcones [33-35]

Recently, following heterogenous catalysts have been successfully used for the synthesis of chalcones and their analogues under ultrasound irradiation:

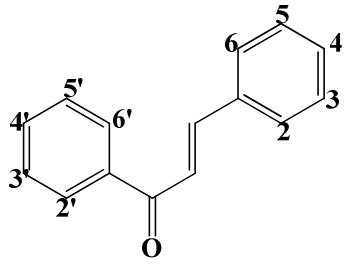
- Potassium carbonate
- Basic Al_2O_3
- Amino grafted Zeolite [36]
- $Ba(OH)_2$
- Pulverized KOH
- KF-Al_2O_3

1.6. Importance of chalcones in organic synthesis

The term chalcone is given to the 1,3-diphenylprop-2-en-1-one framework in which two aromatic rings are connected by an open chain three carbon α,β-unsaturated carbonyl system (1.20) (Figure -2). Chalcones occur in nature as precursors of flavonoids. They are also readily synthesized in the laboratory and structural modifications of the chalcone template are readily achieved. Not many structural templates can claim association with such diverse pharmacological activities in which cytotoxicity, anti-tumour, anti-inflammatory, anti-plasmodial, anti-leishmanial, antioxidant, immune suppression are some examples. In this regard, chalcones can be referred as a privileged structure, a term used to describe selected structural motifs capable of binding to multiple, unrelated classes of receptors or enzymes with high affinity. This chapter describes the rationale of design and synthesis of thiazolylurea containing chalcones.

Numerous pharmacological / pathological and synthetic applications of chalcones[1] have been attracted a great deal of interest to the scientist forum. Therefore, the chemistry of chalcones is considered to be one of the most dynamic and challenging area of chemistry embracing a wide spectrum of advances of both theoretical and

practical relevance. Recently, this work has become main stream of the organic chemistry because of these versatile intermediates could be used as building blocks for the synthesis of highly functionalized heterocycles.



1.20

Figure - 2: Structure 1,3-diphenylprop-2-en-1-one

1.7. Applications of chalcones in organic synthesis

Heterocycles played an important role in medicinal chemistry, serving as key templates to the development of numerous important therapeutic agents. These compounds attracted the attention of chemists and biologists due to their varied nature of physiochemical, pharmacological activities and owing to their involvement in the life sustenance processes. Appreciable number of heterocycles containing nitrogen and oxygen atoms has been turned out to be potential chemotherapeutic and pharmacotherapeutic agents. Various useful synthetic analogs with improved therapeutic properties can be obtained from a single lead compound by structural modification. The same principle is applicable to the various groups of heterocycles derived from chalcones. These heterocycles constitute the major share of synthetic drugs.

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