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Synthesis of Chalcones from Acetone and tetrazole and 2-acetyl naphthalene Assisted by Microwave

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Abstract

In the present study, we understood the total synthesis one chalcone derivative via Claisen-Schmidt condensation of the respective aldehydes and ketones using Microwave assisted irradiation method. In the microwave environment, chemical reactions usually proceed faster and give higher yields with fewer by-products. In the synthesis, a common aldehyde namely tetrazolo {1, 5-a} quinoline-4-carbaldehyde was used while the ketones used were respectively acetone, 2-acetyl Naphthalene. The Chalcone synthesised from Tetrazolo {1, 5-a} quinoline-4-carbaldehyde and acetone was 4-(tetrazolo {1, 5-a} quinoline-4-yl) but -3-en-2-one. The Chalcone synthesised from Tetrazolo {1, 5-a} quinoline-4-carbaldehyde and 2-acetyl Naphthalene was 2E-1-(naphthalene-2-yl)-3-(tetrazolo {1, 5-a} quinoline-4-yl) prop-2-en-1-one. The starting aldehyde was Tetrazolo {1, 5-a} quinoline-4-carbaldehyde necessary for the Claisen-Schmidt condensation was in turn synthesized from Acetanilide which and Vilsmeier reagent (DMF and POCl_3) to produce the intermediate compound 2-chloroquinoline-3-carbaldehyde. This intermediate 2-chloroquinoline-3-carbaldehyde was then treated with sodium azide and acetic acid with ethanol as solvent to produce Tetrazolo {1, 5-a} quinoline-4-carbaldehyde. Structure of the compound were confirmed by spectral data such as IR and $^1\text{H-NMR}$.

Keywords: Tetrazolo, Quinoline, Acetone, Condensation, Microwave Irradiation And Chalcone

Introduction

Organic synthesis is one of a special branch in chemical synthesis and is concerned with construction of organic compounds by reactions. It is believed to be one of the most vital in organic chemistry because the organic molecules contain higher level of complexity compared to pure inorganic compounds. Organic synthesis specifically becomes centre of attraction for many scientists because of the ability to produce beneficial products artificially for human welfare. Organic synthesis has played a very important role in many sectors such as pharmaceuticals, agriculture and others.

On the other hand, development in chemical instruments becomes one of the factors for many researchers to carry their researches more effectively. Advanced technology is able to produce instruments such as NMR, HPLC and others with higher accuracy, higher quality and in less time. The inventions of such scientific instruments promote the organic synthesis sector to widen up the study of interest.

Flavonoids with 1, 3-diarylpropane skeleton can be classified as an outstanding class of naturally occurring compounds (Avila et al., 2008). Chalcones or 1,3-diphenyl-2-propen-1-one derivatives are open chain unsaturated carbonyl system in which two aromatic rings are joined by three carbons having α , β -unsaturated system (Avila

et al., 2008). Chalcones can be considered as the precursors of flavonoids and isoflavanoids (Tomar et al., 2007) and are secondary metabolites of terrestrial plants that exhibit various biological activities (Narender and Reddy, 2007)

Objective of the study

The objective of the study are:

- i. To synthesise Chalcone derivative
- ii. To characterize the synthesized Chalcone derivative
- iii. To demonstrate the importance of microwave assisted synthesis

Methods

Thin layer chromatography (TLC) was conducted using thin layer aluminium plate Merck pre-coated silica gel F254 of 0.2 mm in thickness. The spots were viewed under ultraviolet (UV) light, followed by spraying the plate with iodine. Column chromatography (CC) was performed on silica gel Merck 70-230 mesh.

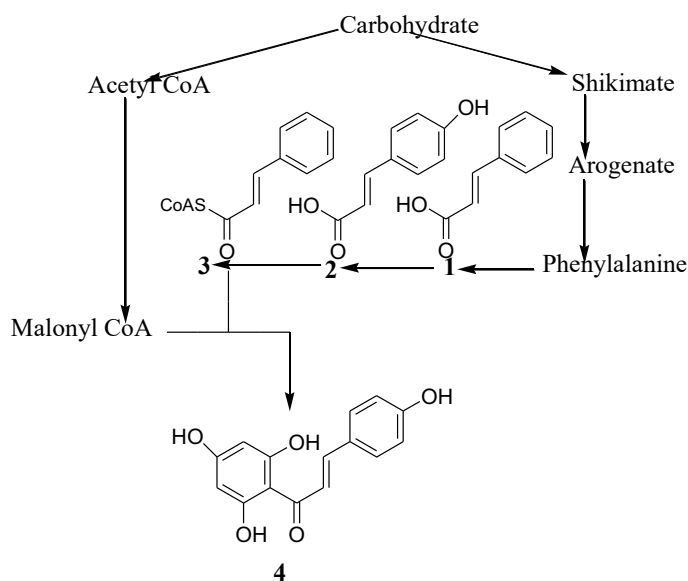
Solvents were purified according to the procedure given in Vogel's Text Book of Practical Organic Chemistry, 5th edition, London. Petroleum ether of boiling 60-80 °C. Several instruments were used to characterize the compound in the experiment. Infrared (IR) spectra were recorded on a KBr pellet. ¹H-NMR was recorded by at 300 MHz and 400 MHz on Varian Gemini Unity Spectrometer using TMS as internal standard.

Microwave assisted synthesis was carried out by using multifunctional microwave system and modified LG microwave oven. The melting points reported were determined in Polmon make instrument.

The starting materials used in this study were commercially available ketones such as acetone, 2-acetyl Naphthalene. Other starting materials was Tetrazole aldehyde which was synthesized in the laboratory from Acetanilide. Other chemicals were acetic acid (CH₃COOH), sodium hydroxide (NaOH), sodium azide (NaN₃), DMF, POCl₃, conc HCl. The organic solvents used were acetone, petroleum ether (PE), absolute ethanol (EtOH), methanol (MeOH), ethyl acetate (EtOAc), hexane, chloroform (CHCl₃).

Biosynthesis of Chalcones

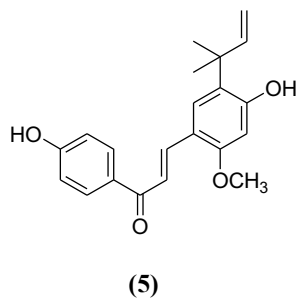
All chalcones derive their carbon skeleton from two basic compounds, malonyl CoA that synthesized from the glycolysis intermediate acetyl-CoA and carbon dioxide, and the CoA ester of hydrocinnamic acid. The aromatic ring B and its adjacent 3-carbon side chain are derived from L-phenylalanine via the Shikimate pathway leading to the formation of the C15 chalcone intermediate. Flavonoids and other compounds associated with flavonoids are derived from this chalcone intermediate by stereospecific action, oxidative rearrangement and other methods. Scheme 1 shows the biosynthesis of chalcone in which the next process after chalcone will lead to the production of flavonoids and its derivative. Cinnamate (1), 4-coumarate (2) and 4-coumaroyl-CoA (3) are involved during the synthesis of natural chalcone (4) (Jenson, 1965).



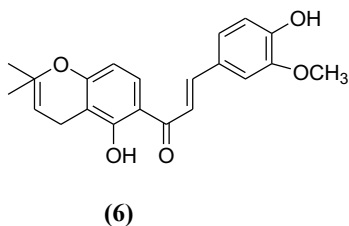
Scheme 1 : The Biosynthetic pathway of chalcones

Naturally occurring chalcone

Naturally occurring chalcone have been reported to have multiple biological and pharmacological activities. The biological activity is mainly depends on the substitution group of chalcones. Licochalcone A (5) is a naturally occurring chalcone isolated from the roots of *Glycyrrhiza inflata* (licorice) which was proved to have in vitro and in vivo antimalarial and antileishmanial activities.

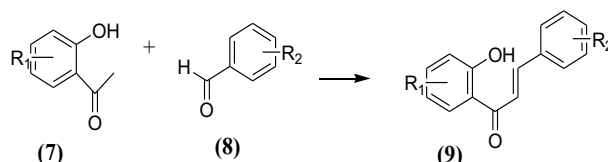


On the other hand 3-methoxy-4-hydroxylonchocarpin (6) isolated from the roots of *Lonchocarpus utilis* inhibits NADH ubiquinone oxidoreductase activity (Avila et al., 2008).



Claisen-Schmidt reaction

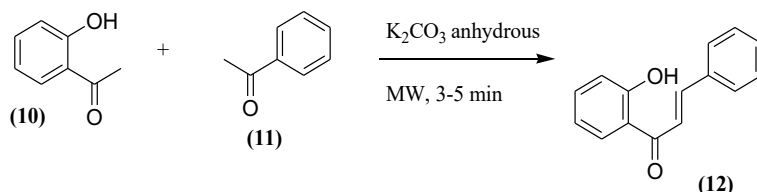
The Claisen-Schmidt condensation between acetophenone and benzaldehyde derivatives is an important C-C bond forming reaction which allows α , β -unsaturated ketone such as chalcones to be obtained (Climent et al, 2004). It is the most frequently used means of establishing the C6-C3-C6 flavanoid nucleus owing to the availability of starting materials such as 2-hydroxyacetophenone (7) and a C6-C1 unit, of benzaldehyde derivatives (8) to obtain a 2-hydroxychalcone (9). Compound (9) bearing A-ring substituent provided by the acetophenone (indicated as R1) and B-ring substituent provided by benzaldehyde (indicated as R2). The classical Claisen-Schmidt reaction is routinely carried out using aqueous sodium or potassium hydroxide or ethanolic sodium at 50°C over a period of several hours. The benzaldehyde derivative is often used in slightly more than equivalent amounts.



Scheme 2 : The Claisen-Schmidt Reaction

Synthesis of Chalcones under Microwave Irradiation

The combination of supported reagents and microwave irradiation can be used to carry out a wide range of reactions in short times and with high conversions and selectivity, without the need of solvents. This approach proved beneficial since it offers several advantages over conventional heating techniques and accelerates the organic reactions (Varma, 1999). The air derived paste of 2-hydroxyacetophenone (10), benzaldehyde (11) and anhydrous K_2CO_3 was subjected to microwave irradiation for 3-5 minutes to produce 2-hydroxychalcones (12). This reaction gave a cleaner product with a high yield (80-90%) (Srivastava, 2008).



Scheme 3: Chalcone synthesis via microwave irradiation

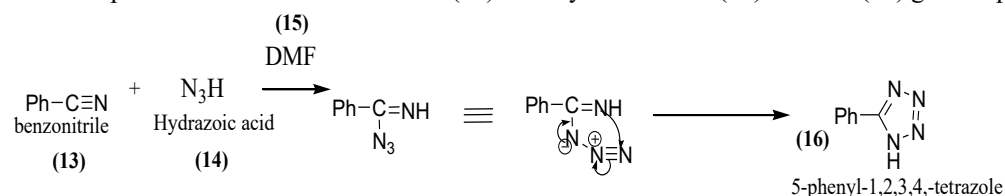
Synthesis of Tetrazoles

There are various ways of synthesizing Tetrazoles. Some of the methods of the synthesis are described below.

By the addition of azide ions to nitriles

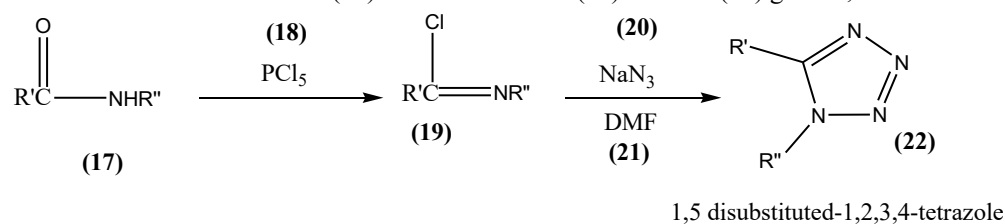
Addition of hydrazoic acid to compounds containing C-N multiple bonds give Tetrazole derivative.

For example: the reaction of benzonitrile (13) with hydrazoic acid (14) in DMF (15) gives 5-phenyl tetrazole (16)

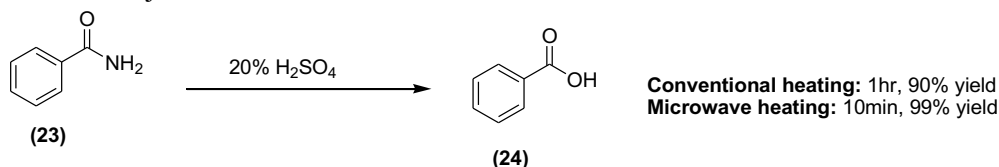


Scheme 4: Reaction of benzonitrile and Hydrazoic acid**From amides.**

Reaction of amides with PCl_5 (18) and sodium azide (20) in DMF (21) gives 1,5-disubstituted tetrazole (22)

**Scheme 5:** Reaction of amide and sodium azide to give tetrazole**Past works on the Microwave assisted synthesis**

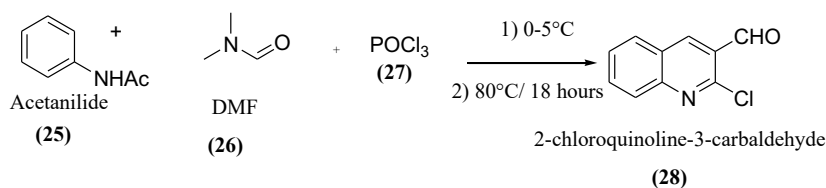
In 1986 Richard Gedye and co-workers published a short communication in Tetrahedron Letters, entitled “The Use of Microwave ovens for Rapid Organic Synthesis” which for the first time described the utilization and advantages of microwave irradiation for organic synthesis. In this original publication four different types of reactions were studied, including the hydrolysis of benzamide to benzoic acid under acidic conditions (Scheme 6). Considerable rate increases (5-1000 fold) were observed for all investigated transformations when compared to classical thermal reflux conditions. The same year, an independent study by the groups Giguere and Majetich describing similar rate-enhancements in microwave-promoted Diels-Alder, Claisen, and even reactions was published in the same journal.

**Scheme 6:** Synthesis of benzoic acid**Results and conclusions**

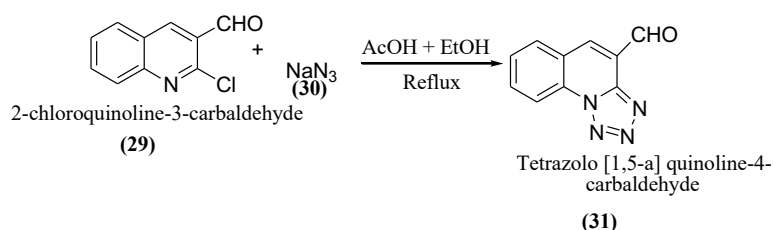
The biological activities that are being discovered in huge number of Tetrazole derivatives prompted us to the Tetrazole aldehyde () as one of the starting material for the synthesis of Chalcones. The chances for the synthesized Chalcones in this way to show biological activity would be higher. The Tetrazole aldehyde (28) was in turn synthesized using a commercially available compound Acetanilide (25) via chloroquinoline aldehyde as an intermediate.

The total scheme of the experimental work up is as follows:

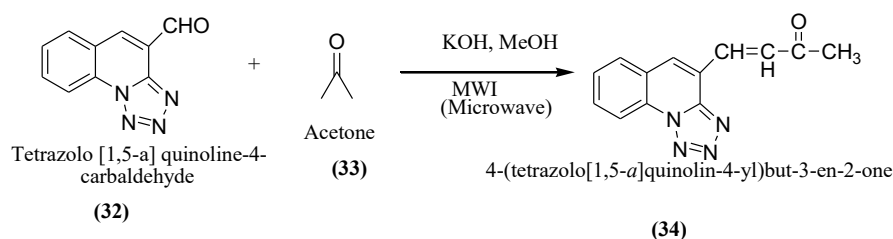
At first, the reaction of substituted amide (DMF) (26) with phosphorus oxychloride (27) is done which gives a substituted chloroiminium ion, also called the Vilsmeier Reagent. The initial product is an iminium ion, which then after cyclizes to give the final product of Quinoline carbaldehyde viz. 2-chloro quinoline 3-carbaldehyde (28).

Step 1: Synthesis of 2-chloroquinoline-3-carbaldehyde

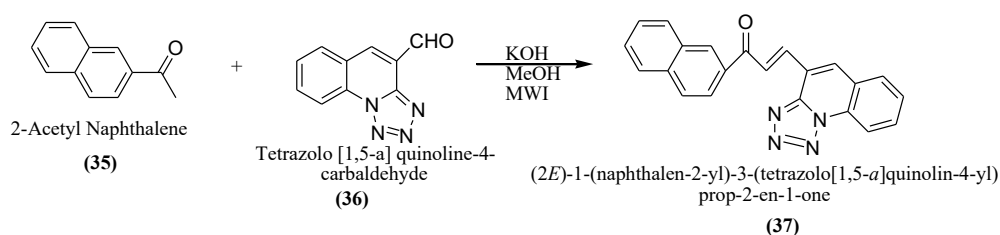
Refluxing the mixture of Quinoline carbaldehyde (29) and sodium azide (30) in ethanol yields the product Tetrazolo [1,5-a] quinoline-4-carbaldehyde (31) which is one the starting material for the synthesis of the chalcones

Step 2: Synthesis of Tetrazole Aldehyde

A mixture of KOH, acetone (33) and Tetrazole aldehyde (32) was kept in a 200 ml beaker and irradiated in a Microwave oven at 180°C for about 10min with the interval time of 30sec. To determine whether the complete reaction took place or not, the reaction mixture was analyzed with the help of Thin Layer Chromatography (TLC) on every 2min of the irradiation.

Step 3: Synthesis of a chalcone from acetone and tetrazole

A mixture of KOH, 2-Acetyl Naphthalene (35) and Tetrazole aldehyde (36) was kept in a 200 ml beaker and irradiated in a Microwave oven at 180°C for about 10min with the interval time of 30sec. To determine whether the complete reaction took place or not, the reaction mixture was analyzed with the help of Thin Layer Chromatography (TLC) on every 2min of the irradiation.

Step 4: Synthesis of chalcone from 2-Acetyl Naphthalene

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