# "BENZYLIC AND ALLYLIC C-H ACTIVATION THROUGH ELECTRON TRANSFER INITIALIZED CYCLIZATION: STRATEGY TOWARDS SYNTHESIS OF TETRAHYDROPYRAN BASED NATURAL PRODUCTS, THEIR ANALOGUES AND STUDY OF THEIR BIOLOGICAL ACTIVITY"

**MINOR RESEARCH PROJECT**

**COMPLETION REPORT**

Submitted to

**UNIVERSITY GRANTS COMMISSION**

**WESTERN REGIONAL OFFICE**

**PUNE – 411007**


Submitted By

**DR. VIJAY M KASTURE**

DEPARTMENT OF CHEMISTRY

MAHARASHTRA EDUCATION SOCIETY'S

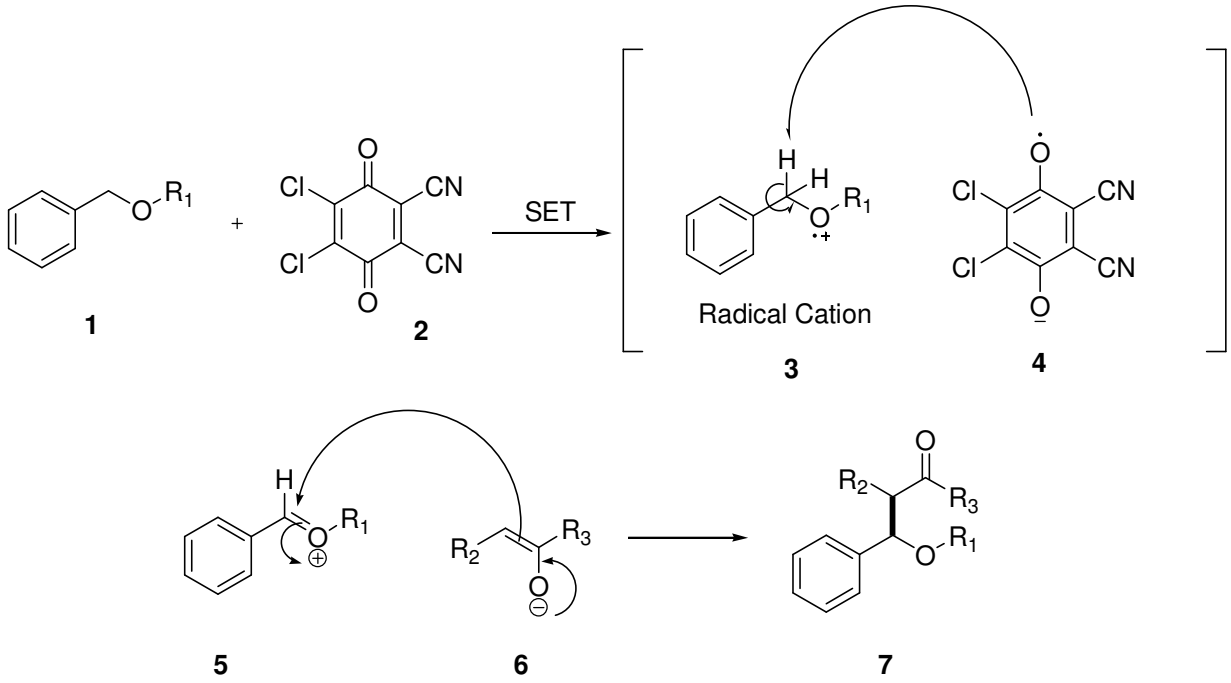
ABASAHEB GARWARE COLLEGE, PUNE - 411004


**NOVEMBER -2018**

## Part A: Electron Transfer Initiated Cyclisation

---

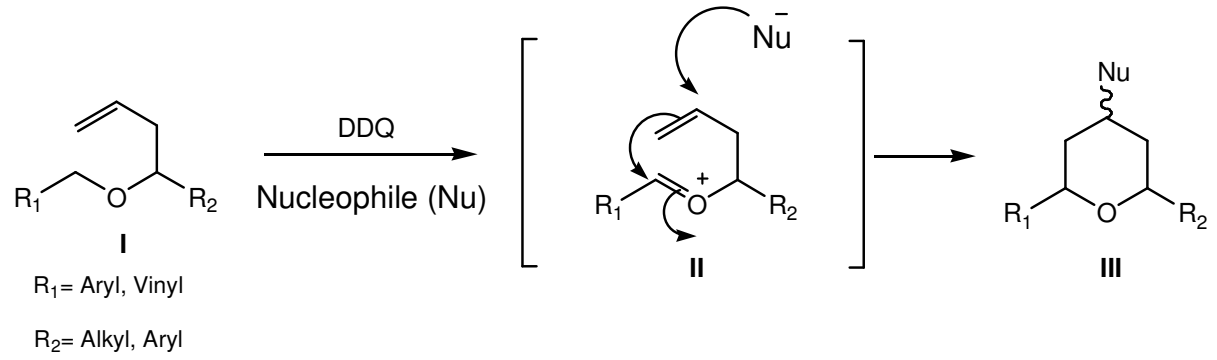
**1.1. Introduction:** Present research work was based on the concept of Single Electron Transfer (SET) process using DDQ as to promote the chemo- and regioselective C-H activation. This strategy was based on the Cross Dehydrogenative Coupling (CDC) though the intramolecular C-C bond formation towards the synthesis of substituted pyranose scaffolds. The thought of this methodology was based on the development of scheme to overcome the challenge associated with $sp^3$ C-H activation. Amongst the metal and non metal oxidising agents, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was considered to be the appropriate electron acceptor for this methodology. The established mechanism for the activation of $sp^3$ C-H is described as follows.




*Scheme 1:* Tentative Mechanism for DDQ mediated direct Cross Direct Dehydrogenative Coupling (CDC)

In this direction, study of oxidative coupling was thought to be performed on properly designed benzylic, allylic or similar reactive substrates. As per the reports, the C-H functionality positioned between heteroatom and the radical stabilising functionalities such as either benzyl or allyl would be helpful for the stabilisation of radical ion. Keeping in mind the potential of DDQ as selective oxidising agent, the strategy was made to utilise the allylic or benzylic ethers **I** in the

construction of intramolecular C-C fond formation through the cross dehydrogenative coupling (CDC). The idea was if the DDQ mediated oxononium ion **II** gets formed, intramolecular nucleophillic attack of double bond results into the cyclisation leads to the formation of C-C bond resulting into pyran ring scaffolds **III**. The synthetic approach was based on the following *scheme 2*.




*Scheme 2*: General Methodology

In this direction, suitably placed $sp^3$ hybridised C-H functionalities were designed and the attempts were made to synthesise these potential substrates **8**-**15** for the electron transfer mediated cyclisation reactions (*Figure 1*).

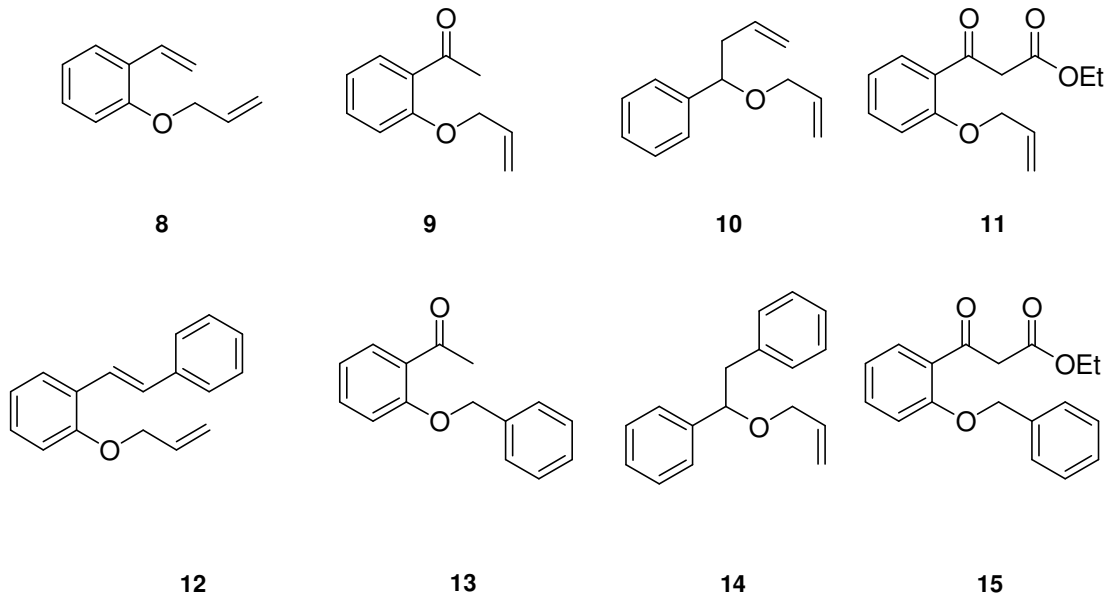



***Figure 1***: Designed substrates for the C-H insertion studies

Barbier reaction was found to be more efficient for the synthesis of homoallylic alcohols. These reactions were optimised to reach upto gram scale. In addition to this, γ-positioned olefin,

γ-positioned carbonyl groups were also synthesised in good yields. Studies were extended for the synthesis of γ-positioned allyl, benzyl substrates and chiral substrates also. Synthetic difficulties were arrived for the synthesis transformation to get these target molecules, such homoallylic alcohols and synthesis of β-keto esters. But, with the number of attempts, we could not achieve the synthesis of all the target compounds.

**1.2. Result and Discussion:** With the successful synthesis of many of the targeted substrates, the key reaction *i.e*. DDQ mediated C-H insertion was performed. The numbers of attempts were made using variation in the mole % of DDQ, use of different nucleophile, solvent systems and reaction conditions (temperature and dilutions). With the multiple procedures, it was difficult to isolate the desired product in the pure form. Most of the reactions were resulted with either no change or resulted with the formation of inseparable complex.

Outcome of the studies:

1) Application of Barbier reaction in the synthesis of homoallylic alcohols on gram scale

2) Protection of homoallylic alcohols with suitable functionalities upto gram scale

3) Characterization of compounds with different spectroscopic techniques

4) Synthesised compounds were studied for intra- and intermolecular cyclisation under variety of reaction conditions.

**1.3. Conclusion:** Number of attempts on the studied examples resulted that, double bond or less reactive inter- or intramolecular nucleophile are not are the efficient candidates to achieve the target scaffolds through the intramolecular C-H bond formation reactions. So, for the intramolecular cyclisation reactions, the nucleophilic centres should be gets released easily as like in the case of *O*- or *C*-silyl protected nucleophile. Such transformations in the present study would be the suggestive route for the proposed outcome.

## Part B: An approach towards The Synthesis Of Conformationallly Locked Chalcones

**2.1. Introduction:** Synthetic organic chemistry has been the constant source for medicinal, biological and the pharmaceutical sciences in getting the new molecules for their challenging work. In one of approaches to get the potential molecules, modification of potential natural and unnatural skeletons with the variations of stereochemistry, functional group and study of their structure-activity relationship is the established protocol. Characteristic scaffolds define the peculiar class of molecules for their specific biological activities. In the view of this, the idea was to modify the established class of molecules by converting the basic skeleton into locked or conformationally rigid. It is acknowledged that the configuration and conformation of organic molecules plays the specific role towards their biological activities.

In the search of simple and small molecules, we found chalcones are the equipped with the α,β-unsaturated aromatic ketones. Chalcones are the vital cores for a number of important biological compounds, which are collectively known as chalconoids (*Figure* 2).

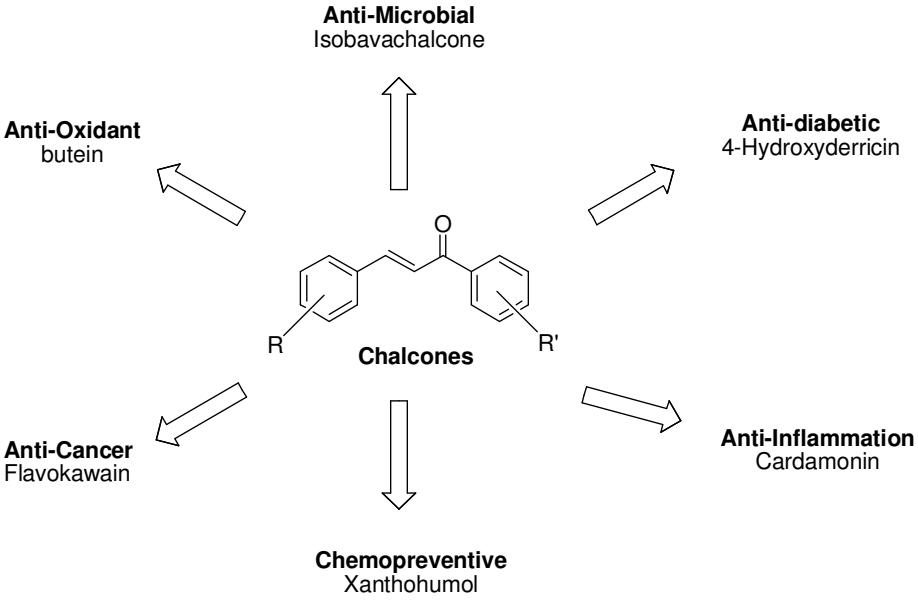



***Figure 2***: Biological significance of Chalcones

I*nteresting* structural advantages of chalcones are the presence of electrophilic as well as the nucleophilic centres, which are the key functionalities to form the cyclic structures. By observing the potential of transferring basic skeleton of chalcones into the objective form, we need to think upon the suitable candidates that could provide the complimentary reactivity of chalcones. In this direction, salicylaldehyde skeleton found to be the appropriate one (*Figure 3*).

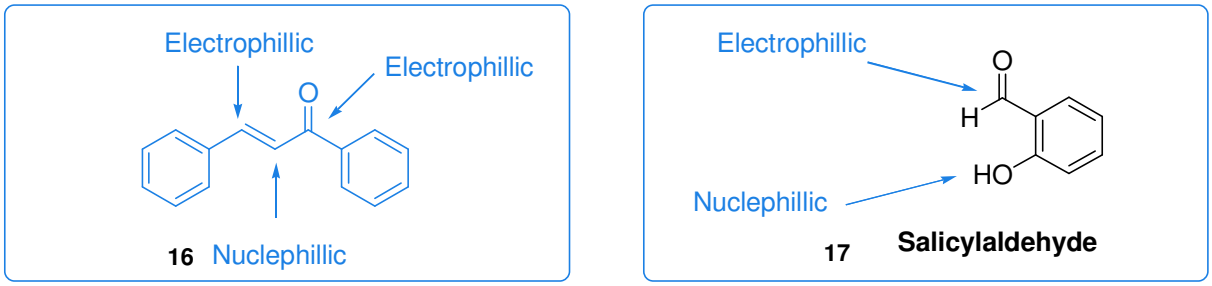



***Figure 3****:* Complimentary reactivities of Chalcone and Salicylaldehyde

So the idea was put forward to transfer the basic chalcones to the cyclic forms in a way that their conformation flexibility gets locked and the structure –activity relationship could be explored using this type of constrained skeletons. The basic design of synthesis of these constrained molecules is describe in following retrosynthetic plan (Figure *4*).

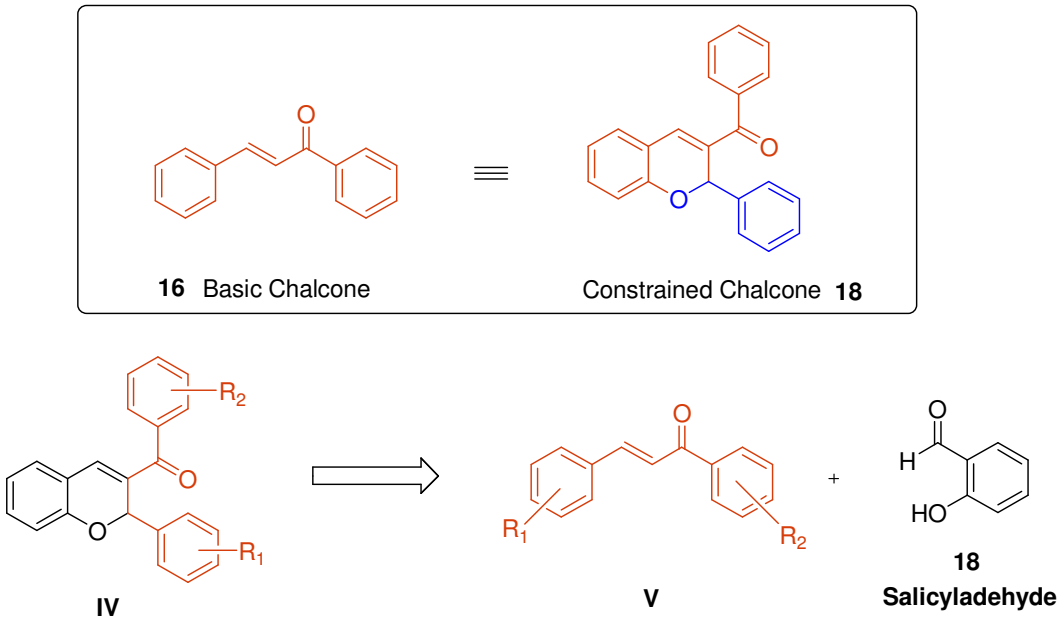
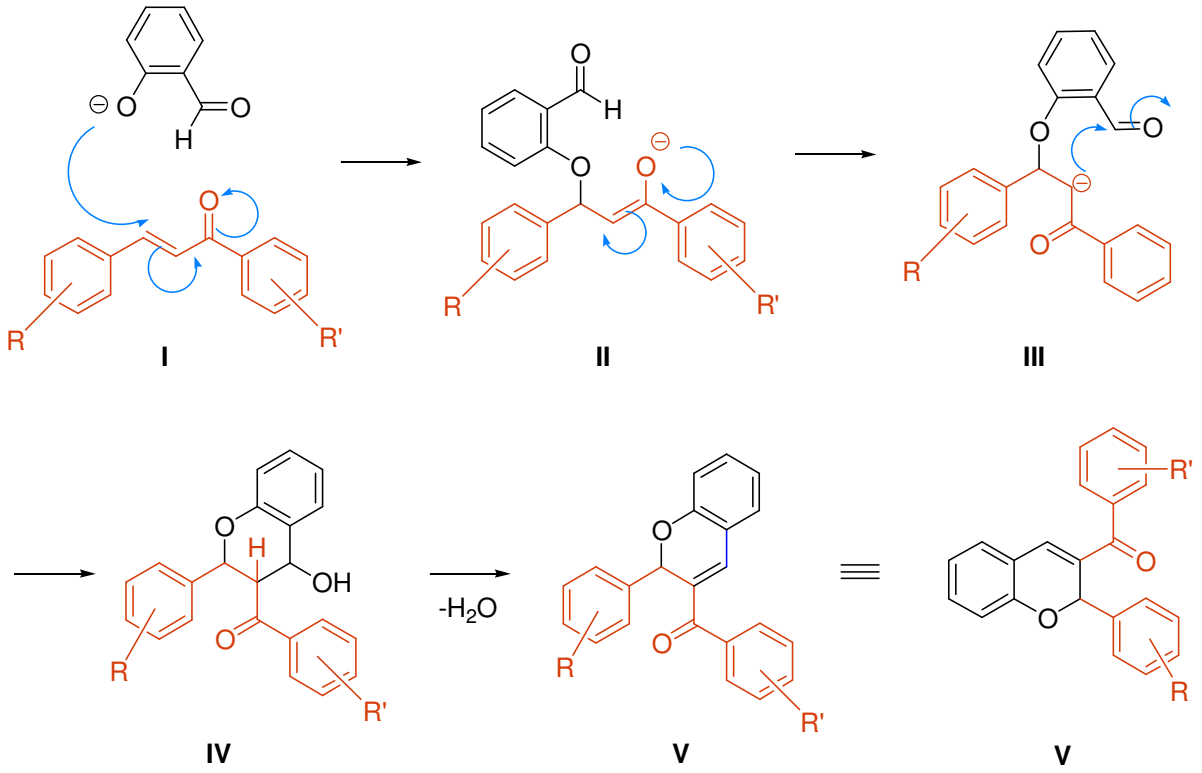



***Figure 4*:** Retrosynthetic Analysis

The general reaction mechanism of base mediated cyclisation between chalcones and the salicylaldehyde could be visualised as follows (*Scheme 3*):




***Scheme 3***: General Mechanism of Cyclisation

**2.2. Result and Discussion:** In the direction of retrosynthetic, we shortlisted some common aldehydes and ketones towards the synthesis of some representative chalcones (*Figure 5*).

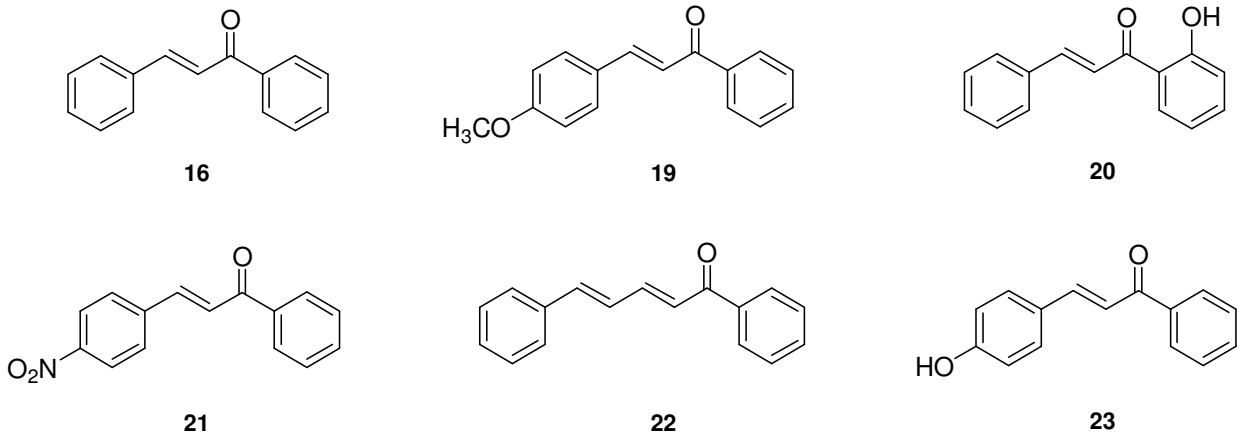
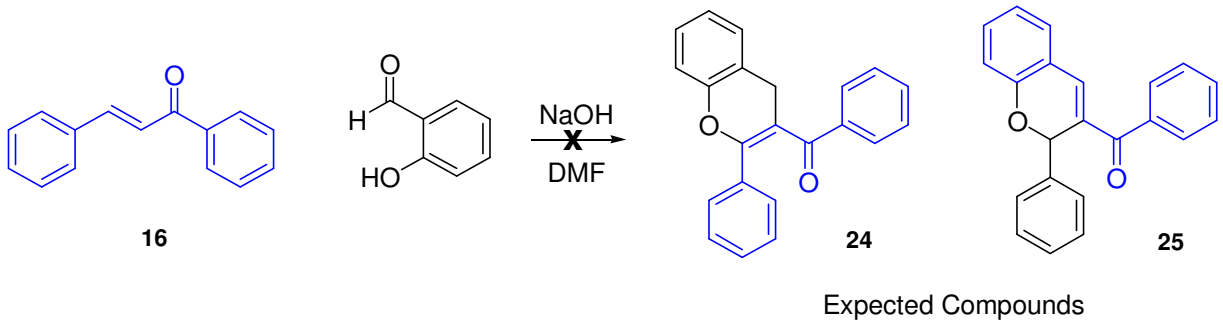



***Figure 5*:** Chalcones substrates for the cyclisation reaction

With the requisite chalcones in hand, the attempts were made in objective to get the cyclisation reaction using different reaction conditions. The anticipated reaction mechanism to

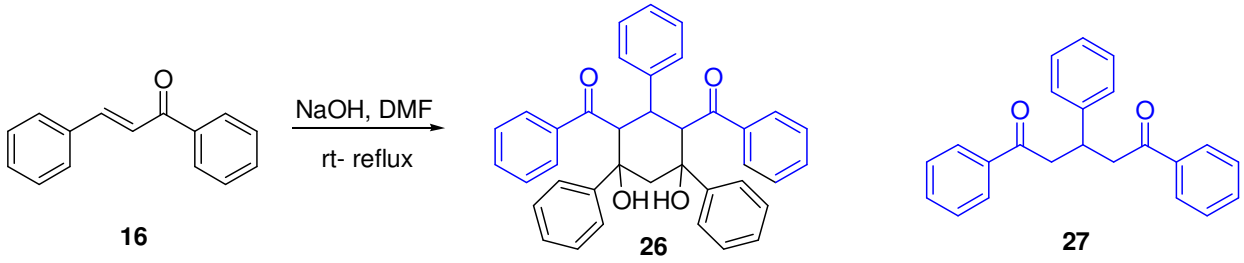
get the desired outcomes is summarised **24** and **25** (isomers). With the number attempts in getting the desired products, different reaction conditions were screened. We attempted different of reaction conditions for the synthesis of target molecules varying bases (LiOH, NaOH, KOH, TEA, DABCO) solvents (MeOH, DMF, $H_2O$), mole equivalents of bases, and different temperature conditions. However, under variety of reaction conditions, we could not control the reaction at the desired stage. Some of the cases, we recovered the substrate while; in some cases the complex mixture was purified to get the more than two to three compounds.




***Scheme 4*:** Cyclisation studies on chalcone

**Doesn't expected the unexpected make the unexpected expected?**

Multiple attempts were made in getting the desired compounds. The isolated compounds were characterised using $^{1}$H-NMR, $^{13}$-NMR and IR. Spectral data was analysed in terms to match the desired compounds. But the spectral data didn't match with the either **24** or **25**. After multiple efforts, we were succeeding to get the single crystals compounds **26** and **27**. Structures were solved and confirmed the structures for **26** and **27.** Spectral data was in the line of confirmed (*Figure 6*).




***Scheme 5***: Cyclisation studies on chalcone

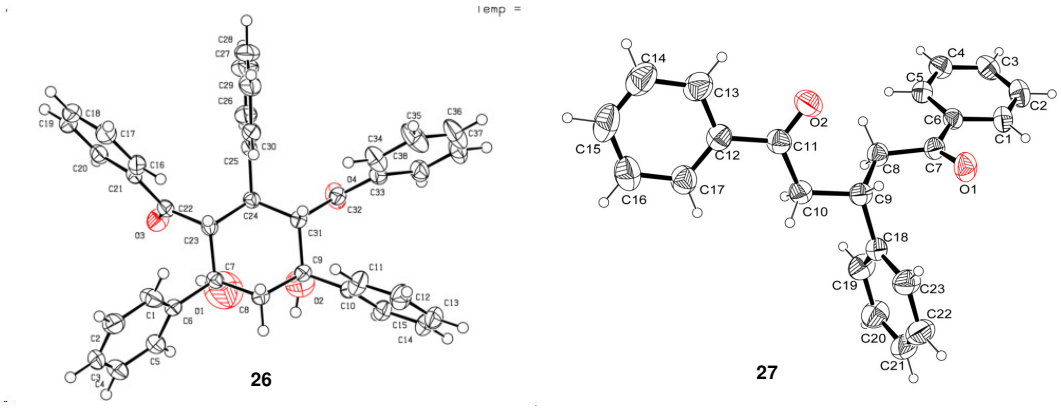



***Figure 6***: ORTEO diagrams of **26** and **27**

In the examination of possible reaction mechanism, literature supports the probable retro-aldol reaction followed by the rearrangement. The likely fragmentation and the intermediates in this reaction are summarised as follows (*Figure 6*).

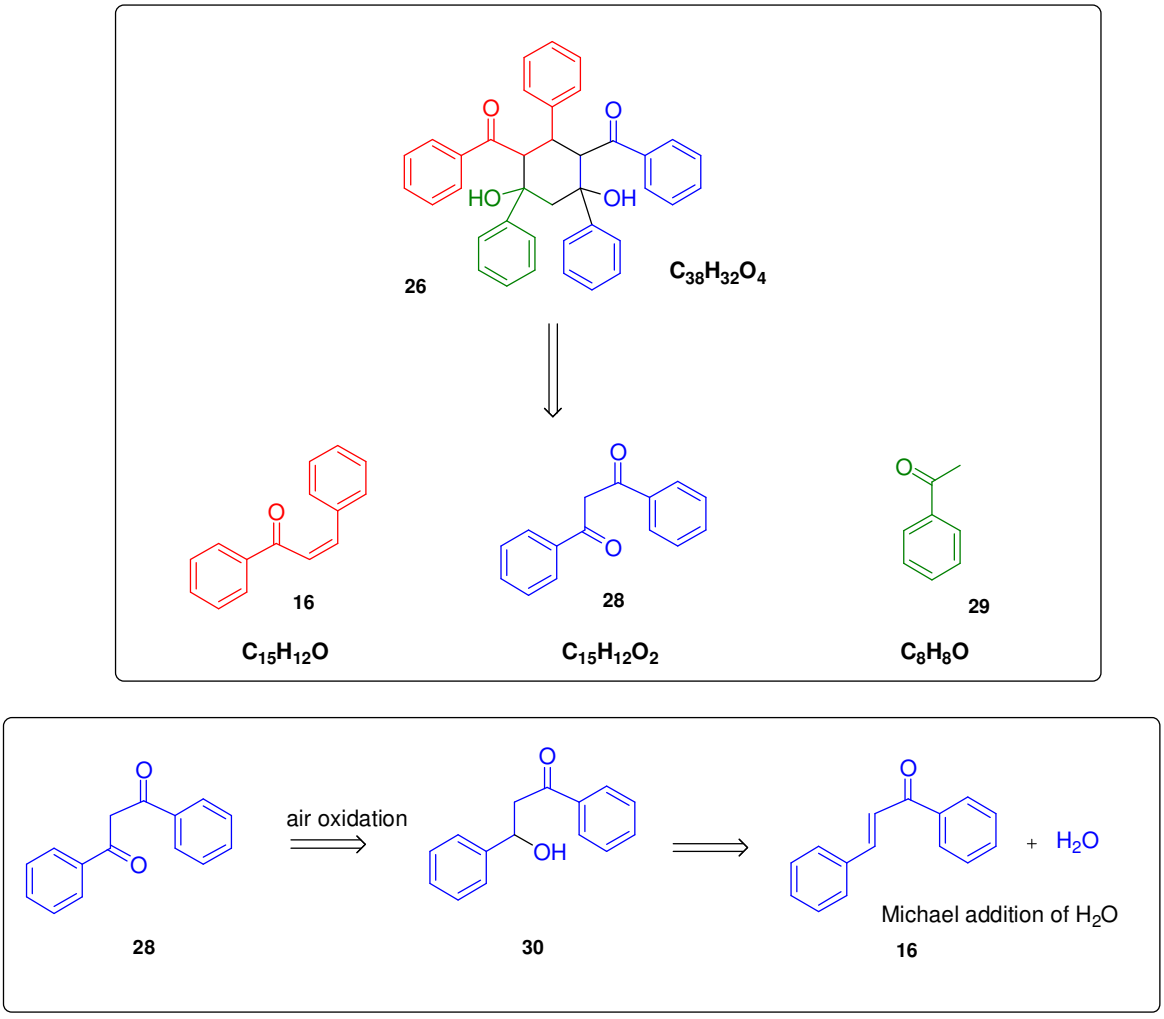



***Figure 7***: Possible Reaction Mechanism Intermediates

Using the similar reaction procedure, chalcones **16-23** were subjected for the similar transformation. These chalcones are resulting into the formation of pentasubstituted cyclohexane-1,3-diol. Work in direction for the confirmation of reaction mechanism as well as the optimisation of products is in progress.

**2.3. Conclusion:** These unexpected results and success in deriving reaction mechanism encouraged us in getting involved with this work. Finding associated with these results are documented to Cambridge Crystallographic Data Centre (CDCC). Mechanistic study of reaction mechanism, biological screening of synthesised products, possible applications of such highly functionalised molecules and the computational studies are under progress. These results would be the fruitful outcome of this project.

**3. Outcome of the Project:**

**1.** Two Novel crystal structures have been submitted to Cambridge Crystallographic Data Centre (CCDC).

For more details please refer to **https://www.ccdc.cam.ac.uk/**

**Crystal Structure 1:**
**CCDC Number: 1845279**

---

Summary of Data CCDC 1845279

---

Compound Name:
Formula: $C_{38}$ $H_{32}$ $O_4$

**Crystal Structure 2:**
**CCDC 1847158**

---

Summary of Data CCDC 1847158

---

Compound Name:
Formula: $C_{23}$ $H_{20}$ $O_2$

(If crystals data will not be submitted in any journal within one year, CCDC will automatically publish in CSD Communications).

**2**. A Mechanistic Study towards the Synthesis of Pentasubstituted Cyclohexane-1,3-Diol (*Manuscript Under Preparation*)