Photo- and Electro-chemical Cyclization of Hydroxychalcones for the Synthesis of Flavonoids

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ABSTRACT

Flavonoids have a broad distribution in the plant kingdom and they display diverse biological and pharmacological properties. Epidemiological studies suggest that the regular consumption of flavonoids protects humans against diseases associated with oxidative stress such as Alzheimer's disease, arteriosclerosis, cancer, and ageing. Therefore, development of methods for the synthesis of flavonoids has high significance in synthetic organic chemistry. With our on-going interest in flavonoid compounds[1] and photo- and electro-chemical catalysis, we have developed two parallel approaches i.e. photo- and electro-chemical cyclization of 2'-hydroxychalcones for the synthesis of flavanones. We have synthesized a set of 2'-hydroxychalcones from the corresponding aldehydes and 2'-hydroxyacetophenones.[2] We optimized the reaction conditions by screening variety of solvents and electrolytes. Reactions monitored by TLC and products characterized using GC-MS.

CHALCONES AND FLAVONOIDS

- Chalcones are abundant in edible plants and are considered to be biochemical precursors of flavonoids.
- So far, over 6000 different naturally occurring flavonoids have been identified. They were classified into flavonols, flavones, catechins, flavanones, anthocyanidins, and isoflavonoids.
- Flavonoids consist of a large class of polyphenolic components that generate pigment in plants and play a biological role in other cellular processes.
- Our attention towards flavonoids was directed by the huge number of epidemiological studies that have been conducted to prove the protective effect of flavonoids against cancer.

PHOTO-& ELECTRO-CHEMICAL CATALYSIS

- Visible light-mediated photoredox catalysis has emerged as one of the fastest growing fields in organic synthesis. Typically, a photoactive catalyst absorbs light in the visible region and participates in single electron transfer processes with organic substrates. This is a mild, economical and environmentally friendly approach to promote radical-based organic transformations and potentially unlock unique reaction pathways.
- Electrochemistry is the study of chemical reactions which take place at the interface of an electrode, usually a solid metal or a semiconductor, and an ionic conductor, the electrolyte. These reactions involve electric charges moving between the electrodes and the electrolyte (or ionic species in a solution).
- Highly energetic intermediates can be generated under mild and precisely controlled conditions.[3]
- Main advantages: Less operational costs, no metal catalysts, oxidants or reductants and thus no waste products.
- As electron transfer takes place on the surface of the electrodes, the choice of material can have a significant impact on the outcome of a reaction.

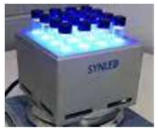
RATIONALE OF THE PROJECT

- Chalcones possess conjugated double bonds and a completely delocalized Π-electron system on both benzene rings. Molecules possessing such system have relatively low redox potentials and have a greater probability of undergoing electron transfer reactions under photo- and electro-chemical reaction conditions.

EQUIPMENT, MATERIALS AND METHODS

- **Equipment:** SynLED Parallel Photoreactor and Electrasyn 2.0 Electrochemical Synthesizer .
- Electrodes: Glassy Carbon and Platinum electrodes.
- **Materials:**
- Electrolytes: Tetrabutyl Ammonium Bromide, Potassium Hexafluorophosphate
- Solvents: Methanol, Acetonitrile, DMF, DME, DMSO.
- Reagents: Aldehydes, 2'-Hydroxyacetophenones, Base
- **Methods**:
- Synthesis of Chalcones
- Photochemical Cyclization of Chalcones
- Electrochemical Cyclization of Chalcones

SynLED Photoreactor

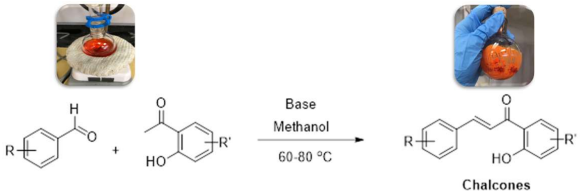


Electrasyn 2.0

SYNTHETIC APPROACHES: RESULTS

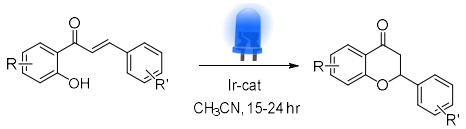
❖ **Synthesis of Chalcones**

- The Claisen-Schmidt condensation of a 2'-hydroxyacetophenones with benzaldehydes afforded the corresponding 2'-hydroxychalcones. (Scheme 1)

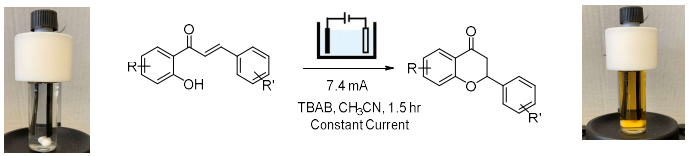


❖ **Conversion of Chalcones to Flavanones**

- Photochemical cyclization of 2'-hydroxychalcones afforded the corresponding flavanones :

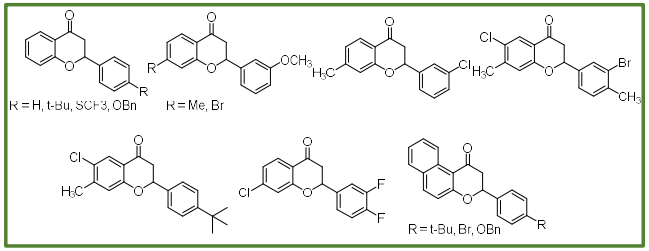


- Electrochemical cyclization:

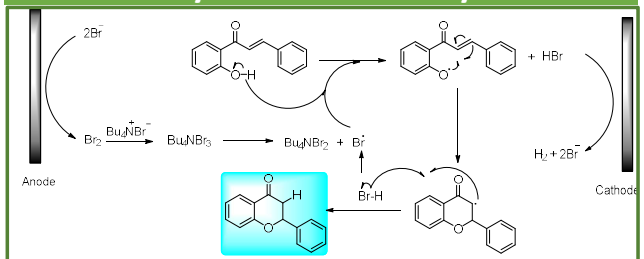


- Reaction Monitoring: Thin-layer Chromatography (TLC)
- Structural Characterization: Gas Chromatography-Mass Spectrometry (GC-MS)

EXAMPLES



Cyclization Pathway



CONCLUSION

- The aim of this project is to develop electrochemical method for the conversion of chalcones to flavonoids.
- Synthesized a set of chalcones from the corresponding aldehydes and 2-hydroxyacetophenones.
- Screened variety of solvents, electrolytes and optimized other parameters including reaction time and current.

FUTURE DIRECTIONS

- Synthesize more examples of chalcones and convert them to Flavanones.
- Develop a one-pot electrochemical cyclization and oxidative process to obtain Flavonol products.
- Conduct biological screening for each compounds and identify the potent molecules.

ACKNOWLEDGEMENTS

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REFERENCES

1. a) Roy et al. Bioorg. Chem. 2021, 107, 104595. b) Roy et al. Data Brief, 2021, 106858.
2. Ahmad, et al. Arabian Journal of Chemistry, vol. 9: 931-935.
3. Yan et al. Chem Rev. 2017 Nov 8;117(21):13230-13319.