INTRODUCTION

Multicomponent reactions (MCRs) have been one of the most efficient strategies in the toolbox of a synthetic organic chemist since centuries. The plethora of synthetic strategies available today can be greatly attributed to MCRs and the limitless possibilities it offers. MCRs have given a rational and easy-to-follow route towards the synthesis of complex scaffolds, bearing importance and applications in the pharmaceutical, agricultural and material sciences. MCRs can be classified into one-pot multistep or domino/ cascade/ tandem reactions, depending upon the sequence of addition of the reactants. This encourages researchers to explore the countless combinations and discover new reaction mechanisms in the process. In addition to this, a solid foundation to the concept of sustainability, which is a topic of discussion and practice among all involved in the process of chemical synthesis, has been provided by MCRs.

Sustainability is a very broad term and can be applied to any area of life. However, when it comes to synthetic organic chemistry, developing greener methodologies for the synthesis of desired molecules is synonymous with sustainable practices. One of the prime initiatives of this domain is the introduction of low cost, recoverable, reusable and easily designed catalytic systems; solvent systems which pose minimal harm to the environment and energy efficient methods of synthesis such as microwave assisted, ultrasound assisted and mechanochemical reactions have become indispensable aids for the scientific community.

The above mentioned methods have been effectively put to use by organic chemists in the synthesis of a wide array of molecules which have revolutionized the modern era. Amongst them, nitrogen and oxygen heterocycles find a significant place. Their importance and utilization in all sectors of life have got them the tags of being highly desirable scaffolds. The resemblance of synthetic scaffolds to naturally present ones only add on to their value. Pyrimidine happens to be one such skeleton, which is present in the very blueprints of life, the DNA and RNA. Thus, incorporating its analogues into complex compounds can prove to be beneficial from the pharmaceutical point of view. We have taken up molecules such as Uracil and barbituric acids as the sources of pyrimidine moiety and tried to incorporate them or utilize them into synthesizing different libraries of compound *via* MCR approaches that essentially involves 5-alkyl/arylidene barbiturate intermediates and an intramolecular cyclocondensation step. This, as well as the greener prospects involved in the reaction routes are the sole focus of the works presented in the thesis.

A total of six (06) novel, greener, economically viable and equally efficient methodologies have been developed and reported in this thesis. The thesis comprises of five (05) chapters and the following sections summarize the contents of each.

OUTLINE OF THE THESIS

Chapter 1: General introduction

The chapter begins with a brief introduction to multicomponent reactions (MCRs) followed by the greener methods of synthesis that have been teamed up with

MCRs towards designing valuable scaffolds. This is followed up a detailed description of 5-alkyl/arylidene barbiturates, its synthesis methods and utilities in the domains of synthetic organic chemistry, which is also the central attraction of all the works described herein.

Chapter 2: On-water multicomponent synthesis of 5-aryl-pyrano [2,3-*d*:6,5-*d'*]dipyrimidinetetraones

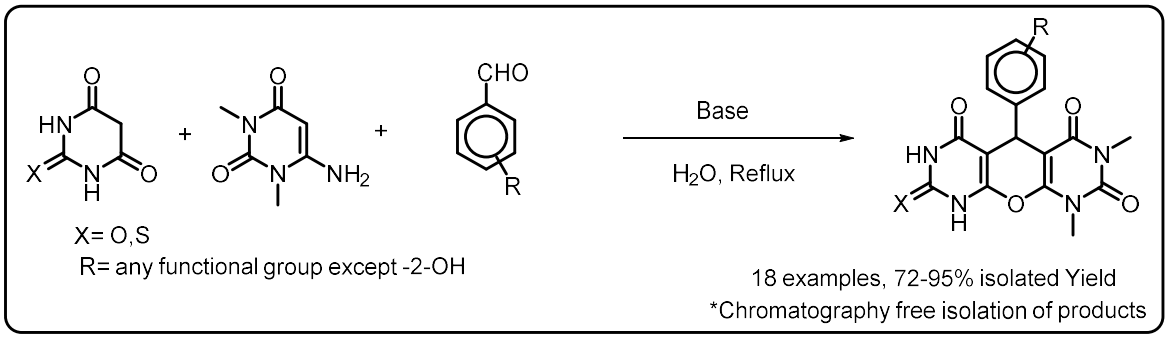
This chapter is divided into two (02) sections and it throws light on the synthesis of unsymmetrical pyrano-di-pyrimidines, which had been less explored. The reactions were carried out “on-water” and the products were isolated *via* “chromatography-free” method.

2.1 *Base mediated “on-water” synthesis of unsymmetrical 5-aryl-pyranodipyrimidine-tetraones.*

In this section a base mediated MCR (tandem) involving 6-amino uracil, aromatic aldehyde and barbituric acid is discussed. It is an “on-water” reaction and takes into account the selectivity of deamination over dehydroxylation in highly basic medium. The reaction proceeds *via* tandem Knoevenagel condensation, Michael addition and selective deaminative annulation. Moreover, the synthesis of unsymmetrical 5-aryl-pyranodipyrimidine-tetraones is the main attraction of this work. The schematic representation of the reaction is shown in Scheme 2.1.

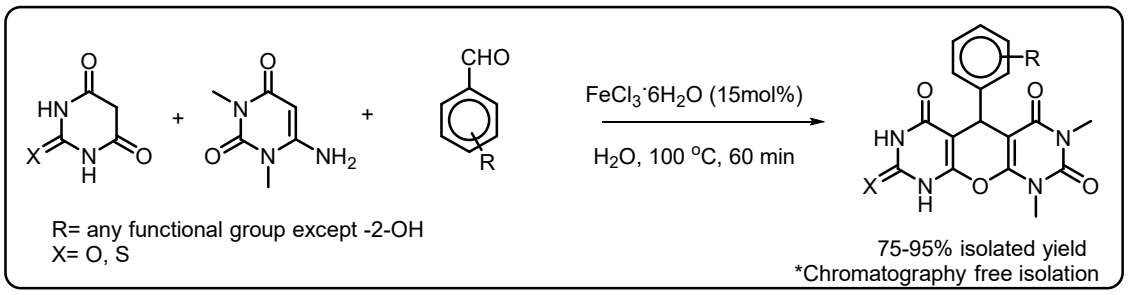
2.2 *$FeCl_3{\cdot}6H_2O$ catalysed “on-water” synthesis of unsymmetrical 5-aryl-pyranodipyrimidine-tetraones*

This work is a modification of the base mediated reaction described earlier. The difference is that we have eliminated the requirement of stoichiometric amount of



Scheme 2.1: Base mediated "on-water" synthesis of unsymmetrical 5-aryl-pyranodipyrimidine-tetraones

base and successfully designed the catalytic route. It is a run-against-time tandem reaction where the rate of two different reactions, *viz*; the conversion of 6-aminouracil to barbituric acid in the presence of $FeCl_3{\cdot}6H_2O$ and water at elevated temperature and the Knoevenagel condensation of barbituric acid and aromatic aldehyde, are taken into account. The subsequent reactions that take place in tandem are the Michael addition of the 6-aminouracil derived barbituric acid to the Knoevenagel product followed by dehydroxylative annulation. The reaction scheme is as follows:



Scheme 2.2: $FeCl_3{\cdot}6H_2O$ catalysed "on-water" synthesis of unsymmetrical 5-aryl-pyranodipyrimidine-tetraones

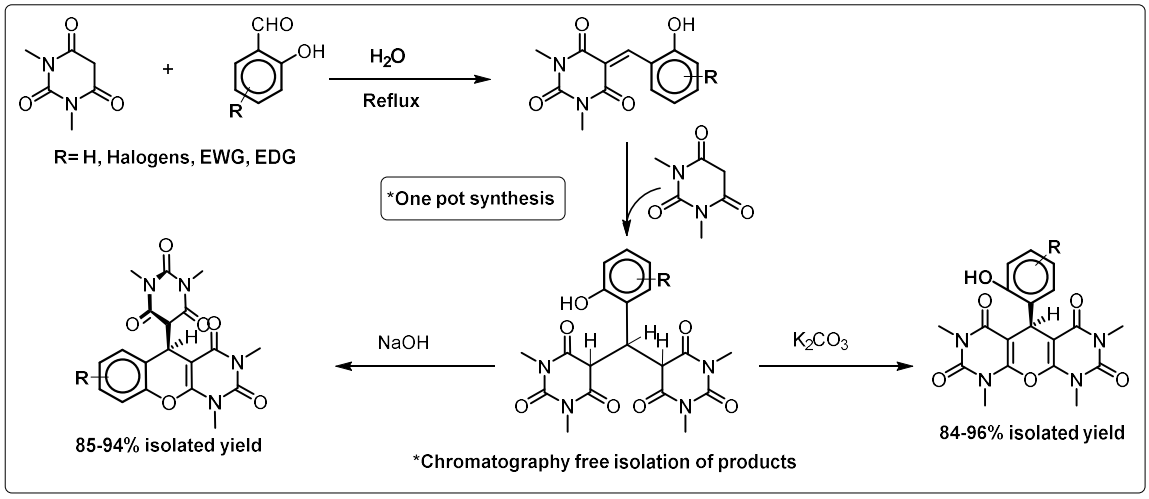
Chapter 3: "On-water" synthesis of heterocycles functionalised chromenopyrimidines from benzylidene barbiturates of 2-hydroxy benzaldehydes

The limitations that were faced in Chapter 2 were approached from a different angle and the encouraging results that came forward helped in designing two

methodologies for the synthesis of benzo/heterocycle functionalised chromenopyrimidines. The reactions were carried out in aqueous media and the products were isolated *via* simple filtration. This chapter is divided into two sections:

3.1 *Base controlled selective synthesis of barbiturate functionalised chromeno[2,3-d]pyrimidines and 5-arylpyranodipyrimidines from benzylidene barbiturates of 2-hydroxybenzaldehydes*

In this part the strength of different bases were taken into account and how that determined the chemoselectivity of the reactions that followed, was studied. NaOH and K_2CO_3 behaved differently when faced with two different types of acidic protons present in the product formed *via* Michael addition of barbituric acid and 2-hydroxybenzylidene barbiturates. While NaOH showed preference towards the phenolic proton, K_2CO_3 abstracted the acidic methylene proton. Such selectivity resulted in the formation of two different products from the same starting materials.



Scheme 3.1: Base directed synthesis of barbiturate functionalised chromeno[2,3-*d*]pyrimidines and symmetrical pyranodipyrimidines

3.2 *Iodine-acetic acid catalysed synthesis of 6-aminouracil, 4-hydroxycoumarin, and barbituric acid functionalised Chromeno[2,3-d]pyrimidines*

Iodine-Acetic acid was found to be an excellent catalytic system for the synthesis of three different classes of chromenopyrimidines bearing different heterocyclic substituents. The reaction was highly selective and showed tolerance towards various functional groups, thereby exhibiting the robustness as well as the selectivity of the catalyst and the reaction protocol. Additionally, the products precipitated out upon formation and therefore eliminated the tedious steps of chromatographic separations. The schematic representation of the reaction protocol is shown in scheme 3.2.

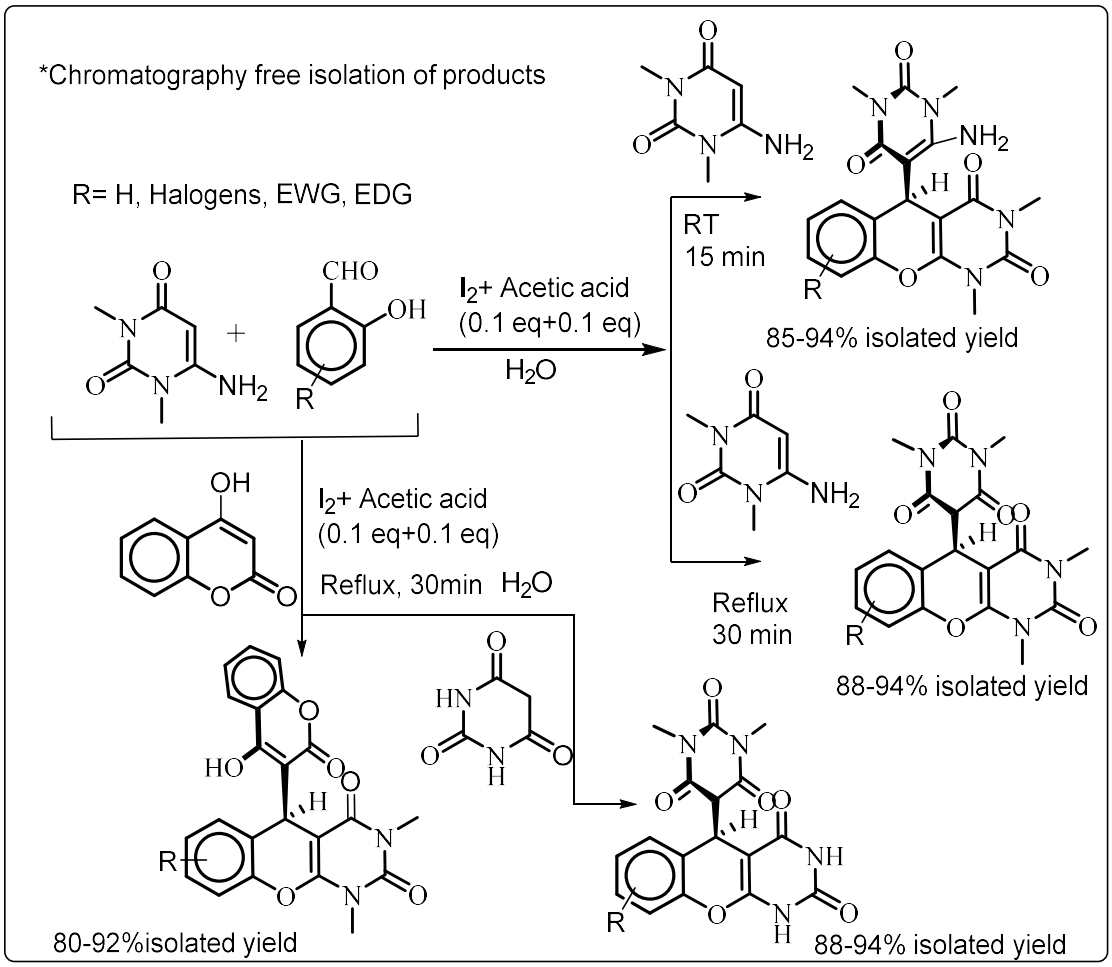
Chapter 4: Development of greener methodologies for the synthesis of 5-aryl/spiro-[1,2,4]-triazolidine-3-thiones

In this chapter some conventional nucleophiles and the consequences of their addition to alkyl/arylidene barbiturates under different reaction conditions is discussed. It is divided into two (02) sections.

4.1 *Synthesis of 5-aryl/spiro triazolidone-3-thiones via Liquid Assisted Grinding and "on-water" methods*

The liquid assisted grinding (LAG) methodology for the one-pot synthesis of 5-aryl/spiro-1,2,4-triazolidie-3-thiones is a fast and environmentally benign protocol, where there is near to zero waste of chemicals, and which also holds the prospect of expanding the domains of homogeneous recyclable reaction media.

In addition to this, a protocol for the "on-water" synthesis of the mentioned class of compounds was also developed, which proved to be equally potent, despite taking comparatively more time. Moreover, there has been a revisit to the

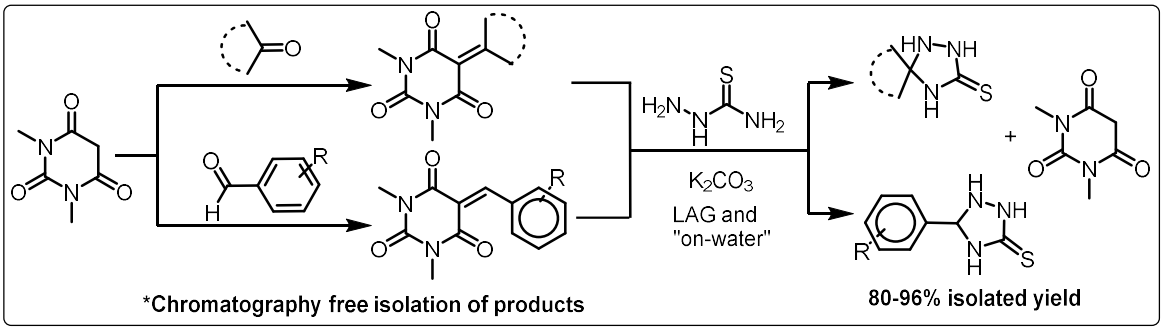


Scheme 3.2: Iodine-acetic acid catalysed synthesis of 6-aminouracil, 4-hydroxycoumarin, and barbituric acid functionalised chromeno[2,3-*d*]pyrimidines

mechanism of the reaction, which has been explained in accordance with experimental observations. This reaction goes through tandem nucleophilic addition of thiosemicarbazide to the alkyl/arylidene barbiturate, followed by cyclisation and rearrangement of the intermediate cyclised product. The reaction scheme is as follows:

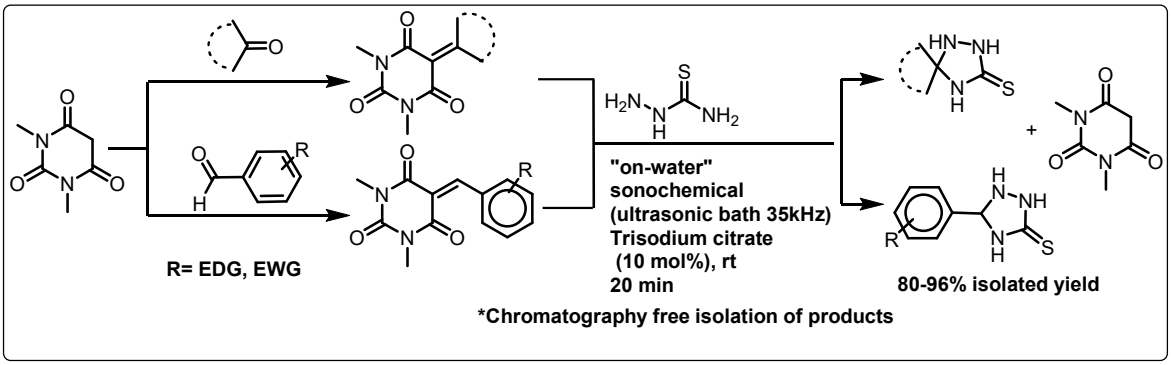
4.2 *Trisodium citrate dihydrate catalysed "on-water" synthesis of 5-aryl/spiro triazolidone-3-thiones via ultra-sonication*

In this section, 5-aryl/spiro-1,2,4-triazolidie-3-thiones have been synthesised with the help of trisodium citrate dihydrate acting as catalyst. The reaction is ultrasound assisted and is a considerably efficient modification of the base



Scheme 4.1: Synthesis of 5-aryl/spiro triazolidone-3-thiones via Liquid Assisted Grinding and "on-water" methods

mediated mechanochemical or "on-water" method. The substrate scope of the reaction protocol has been extended to 2-hydroxy-aryl aldehydes, which also shows the wide range tolerance of functional groups as well as the selectivity of the reaction protocol. The reaction scheme is shown in scheme 4.2.



Scheme 4.2: Trisodium citrate catalysed "on-water" synthesis of 5-aryl/spiro triazolidone-3-thiones *via* ultrasound assisted method

Chapter 5: Conclusion

This chapter summarises the findings of all the works and contains a brief conclusion to the work as a whole. Also included in this chapter are the future scopes of the entire work.

The following are the outcomes of the works presented in the thesis:

[1] Six (06) "on-water"and green MCR methods for the synthesis of *N*- and *O*-heterocycles were developed.

[2] The reaction protocols effectively provided products with good-excellent yields and with high purity.

[3] The isolation of products did not require any chromatographic method (simple filtration was enough).

[4] High chemoselectivity and regioselectivity was observed.

[5] Plausible mechanisms for each protocol were deduced on the basis of experimental findings and existing theories.

[6] Corrections were made to existing mechanisms on the basis of experimental findings.

[7] All the products were characterised with the aid of NMR spectroscopy and other analytical techniques.