Chapter 1

General Introduction

INTRODUCTION

1.1 Multicomponent Reactions

Multicomponent reactions (MCRs) can be defined as the one pot reactions where three or more components are introduced at once, to form a product containing a majority of the constituent atoms present in the reactants. Thus, such protocols encompasses as a series of chemical transformations without bearing the necessity to change the “pot” after each conversion. This enables to achieve the creation of diverse molecular structures and create libraries of compounds within less time and helps in by-passing the efforts required in step-by-step synthetic procedures [1]. This has resulted in the MCR protocols attaining the centre stages in pharmaceutical industries, where libraries of compounds having probable biological activities are tested day in and day out. Some of the molecules having biological utilities are shown in **figure 1.1** [2]. The onus of these protocols does not end here, as the number of publications and patents related to MCR technology have also increased manifolds in the last couple of decades, thereby showing the engagement of a multitude of synthetic chemists in the development of different strategies for the synthesis of molecules with complex structures, in a simpler way.

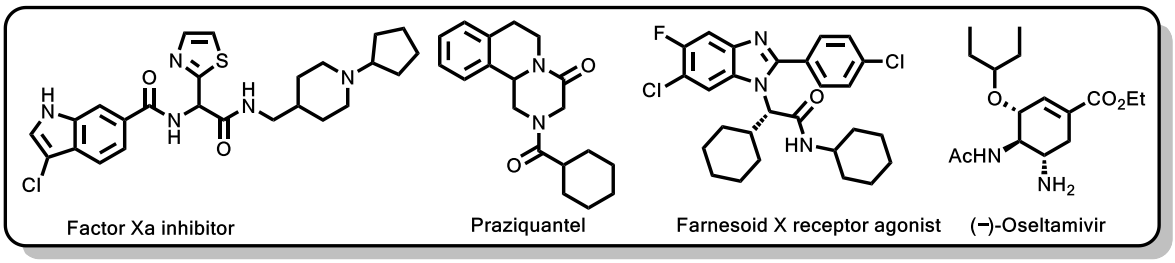


Figure 1.1 Examples of drugs synthesized with the help of MCR strategy: factor Xa inhibitors [3], praziquantel [4], farnesoid X receptor agonists [5], and (–)-oseltamivir [6]

The development of MCRs has also brought in the concept of overlapping the protocols with sustainable chemistry and has been synonymous with the principles of green chemistry. The terminologies such as eco compatibility, atom economy, and pot-economy have seen wide spread implications in the realms of multicomponent reactions [7-9].

Checking into the history of MCRs has revealed that the Strecker reaction (1850) can be taken into consideration as the first reported MCR [10] and since its inception a great number of interesting MCRs have stood out as classics of MCRs. It is on these reactions that the modern day MCRs are planned or derived. Some of the most significant ones are: Hantzsch 1,4-dihydropyridine synthesis (1891) [11], Hantzsch pyrrole synthesis (1890) [12], Biginelli reaction (1891) for the synthesis of dihydropyrimidones [13], Mannich reaction (1917) for the synthesis of β-amino carbonyl compounds [14], Robinson annulation (1917) for the synthesis of tropinone [15], Passerini reaction (1921) for the synthesis of α-acyloxy amides [16], and the Ugi reaction (1959) for the synthesis of α-N-acylamino acids [17]. In recent times asymmetric MCRs have caught the interests of many and this has led to the development of quite a number of asymmetric catalysts, thereby, leading a way for merging different domains of synthetic chemistry [18].

1.1.1 Synthetic approaches in MCRs

There is no definite boundary to the approaches that can be made to designing MCRs. Depending upon the limitations of the reactants used, conditions that needs to be applied or the desires of the researcher in making the methodology greener, several strategies have emerged. **Microwave (MW) radiations** have come up as an excellent substitute to conventional heating reactions. The MW

radiations has a huge advantage over normal heating methods because when a polar solvent media is used, the heating of the reaction media is more efficient and requires very less time for completion [19]. Another strategy that has been taken up to obtain better results is **ultra-sonication**. Ultrasound irradiations are useful in multiphasic systems, where the starting materials of a particular reaction are nearly insoluble in the reaction media or when there is generation of volatile gases during the reaction or in cases where radical or ionic species are involved [20]. **Solid-phase synthesis** is another strategy that has proven its utility in many MCRs [21]. In this method, the final products adhere to a solid support and collected *via* simple washing steps after the removal of the by-products. This simplifies the post reaction work-up process, as it requires only simple filtration for the isolation of pure products and thereby bypasses tedious chromatographic techniques. This saves time as well as valuable resources. Also, in multicatalytic MCRs, this technique has helped in maintaining the goals of one-pot strategy. Again, when combined with automated reaction preparation system, solid-phase synthetic procedures have become the go-to protocol for the easy and rapid creation of various libraries of compounds [22].

Infrared (IR) and **photochemical irradiations** are some upcoming methods brought into effect for MCRs. However, these approaches can be successfully employed in situations where the reactants absorb these specific radiations to participate in a reaction with other reagents. Therefore, the reports on such methodologies are limited [23] but that does not hinder further research to reveal the new prospects and potential ways of synthesising complex molecules.

1.1.2 Green chemistry in MCRs

To a large extent MCRs have been in fine agreement with the basic concepts of green chemistry which were set up by Anastas and Warner in 1998 [24]. Formation of complex products in one pot through modified synthetic strategies is environmentally benign as there is conservation of resources, reduction in energy requirements and substantial reduction the generation of wastes. Thus, MCRs have become the centre of attraction to those researchers who target development of green processes of synthesis. In this section we shall discuss about the ways MCRs have ticked the boxes of being green protocols.

a) Atom economy

Atom economy is the measure of the efficacy of a reaction by establishing a comparison between the amounts of target product formed to the amount of by-products generated [11]. To be more atom-economic, it must be ensured that a majority of the reactants are incorporated into the desired molecule. If the design of a complex molecule is carried out in a step wise fashion (multi-pot), the efficacy is lost in the process of transfer and isolation. MCRs provide an excellent platform to achieve this as different molecules are efficiently combined in a single pot to constitute a complex product. Thus, development of MCRs can be synonymously used for development of atom-economic protocols.

b) Usage of green solvents

Solvents are an indispensable part designing a synthetic route. Their nature has been a matter of concern in recent times and search for greener alternatives to the ones which pose hazard to the environment or to human health has been actively taken up by researchers around the globe. It is desired to perform and accomplish a reaction in environmentally friendly solvents and if possible reuse or

recycle them efficiently. Water [25], ionic liquids [26, 27] and various bio based solvents [28] have been extensively used in MCRs. They are environmentally benign and in many a case, have exhibited fascinating properties leading to unprecedented results, which would have been difficult to obtain with other solvents. Since the reaction protocols reported in this thesis have been accomplished in aqueous media, therefore we shall discuss in detail the usage of water as green solvent in MCRs.

MCRs in aqueous media

Termed as the *lingua franca* of life, water happens to be the solvent of choice of the nature, where all the biochemical reactions and the life processes take place [29]. Contrastingly, this is not always the case while designing complex organic compounds in the laboratory. Where on one hand, complex biological molecules take shape and attain specific geometries in aqueous and oxygenated environment; on the other hand a lot of organic reactions carried out in academic laboratories and industries do not even proceed by a marginal percentage under such conditions. Thus, mimicking nature takes a hit while attempting to create some chemical bonds. Therefore, researchers from time immemorial have sorted to rely on highly reactive reagents to gain the control over chemical reactivity and channelize the chemical reactions down the desired routes. Nevertheless, chemical transformations accomplished in aqueous environments are also not unheard of. It is quite common and the earliest reports can be traced back to the urea synthesis by Wöhler in 1828 [30]. However, if we consider the scenario from the perspective of an organic chemist, then, perhaps the synthesis of indigo by Baeyer and Drewsen in 1882 could suffice as an aqueous media reaction [31]. Water possesses several unique properties, both physical and chemical, such as

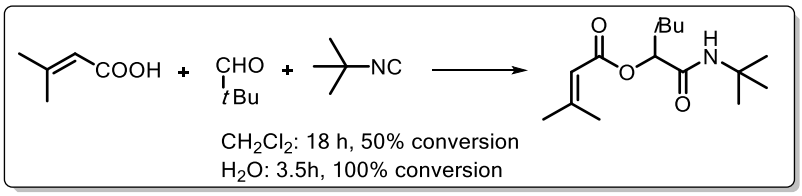
wide spread hydrogen bonding, high heat capacity and dielectric constant, optimum solubility factor for gases like oxygen and carbon dioxide and sufficiently large temperature window that allows it to remain in the liquid state. These distinctive properties arise due to the structure of the water molecule [31, 32]. The studies made on the structure have brought to light enough theoretical evidences to draw the models to explain how water enhances the rate of some organic reactions too. Notwithstanding the potential advantages of water, it has still failed to be the sole solvent of choice for organic synthesis because many organic compounds are not soluble in it and if we follow the common notion "*corpora non agunt nisi soluta*", meaning that a reaction will not take place until and unless the reactants dissolve, it becomes hard to convince the masses about the feasibility of the reaction. Despite such common notions doing circles in the research community, "aqueous reactions", where water is used along with an organic co-solvent to increase the solubility of the reactants have surfaced quite often [33, 34]. Alternatively, the introduction of polar functional groups to the reactants leading to increasing its hydrophilicity has also been explored to make the reactants at least partially soluble in water [35]. However, manipulation such as these only diminishes the wide spectrum of advantages that water holds over traditional organic solvents. Water is cheap, offers simplicity to the reaction conditions and makes post reaction workup easy along with ease of isolation of the products. Therefore, the current scenario of organic synthesis covers a plethora of organic reactions being carried out in aqueous media. The solubility of reactants and the products have been not given a priority because it has been observed in literature that it can range from completely soluble to partially soluble to practically not soluble. Hence, the reaction mixture can be both homogeneous

and heterogeneous. Even the amount of water used for the reactions can vary from being used in stoichiometric amounts to large volumes where the reactants are either suspended or dissolved. As a matter of fact, terminologies such as “in water”, “in the presence of water” and “on-water” are quite common in recent publications [36, 37]. This has also lead to the development of several cases of micellar catalysis with the help of non-ionic surfactants such as PTS, Triton-X and Aliquat-336 [38-40]. As an attempt to extend our research in the field of “*on-water*” reactions, herein the thesis we have tried to develop some multicomponent reaction protocols using water as the sole solvent.

The definition of “*on-water*”, as stated by Sharpless and co-workers is a situation when insoluble reactants(s) are stirred in aqueous emulsions or suspensions without the addition of any organic co-solvents [41]. However, as seen in many cases it is quite impossible to ascertain whether the reaction is happening in or on-water but as long as the heterogeneity of the reaction mixture is maintained and the overall reaction benefits from such a situation, it qualifies as “*on-water*”. In short, the moniker should reflect the defining attribute of the reaction, i.e. the lack of solubility of the reactant in water. It is observed that there is a considerable increase in the rate of the reaction when carried out in water. However, it cannot be attributed to the sole factor that while the reaction is being carried out on-water, there is an increase in the concentration of the reactants, because on-water reactions have even shown accelerated rates in comparison to neat reactions. We must also understand the fact that while accelerating the rate of a reaction is not the sole attribute of these reactions because, even if this factor is modest, water can be used for other advantages. Firstly, water has a very high heat capacity and therefore acts as an excellent heat sink, which

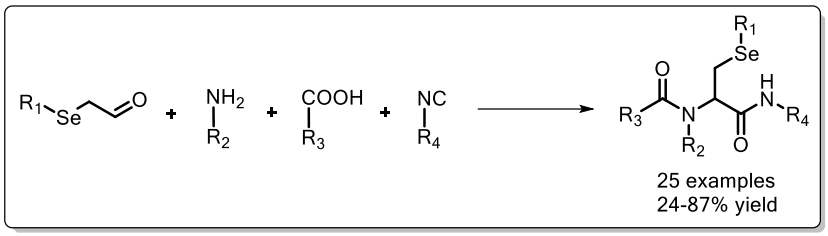
makes exothermic reactions safer and offers a high degree of selectivity when carried out in large scale. Secondly, on-water reactions have water insoluble reactants and these obviously lead to the formation of water insoluble products. This simplifies their isolation process, which is either a simple filtration for solid products or phase separation for liquid products. Thirdly, the growing number of reports of attaining high degree of selectivity by carrying out the reactions on-water underlines the potential for intensification of the processes carried out on-water [42].

From the MCR point of view, the classical Ugi and Passerini reactions are great examples to begin with. Pirrung and Sarma's work on the Passerini reaction carried out on-water clearly demonstrates the notable enhancement in the conversion rate as well as the rate of the reaction on-water as compared to dichloromethane (**Scheme 1.1**) [43].



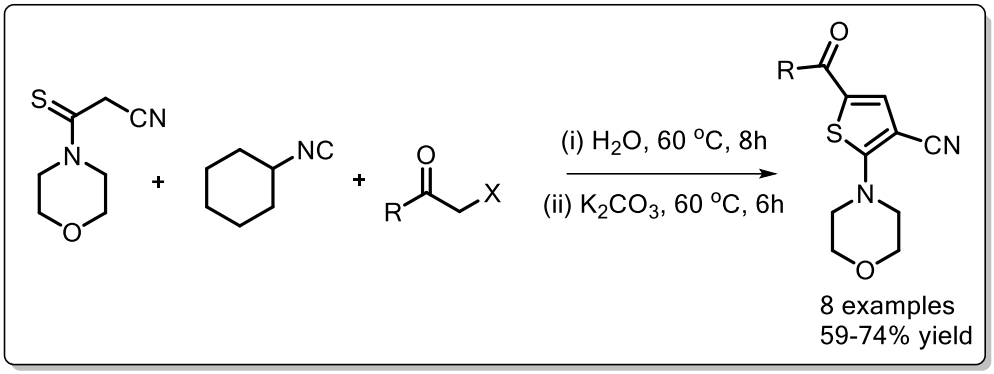
Scheme 1.1 Enhancement of reaction parameters of the Passerini reaction performed on-water (Pirrung and Sarma)

The seleno version of the Ugi reaction developed by Wessjohann and coworkers was carried out on-water to afford seleno amino acids in variable yields (24-87%) (**Scheme 1.2**) [44].



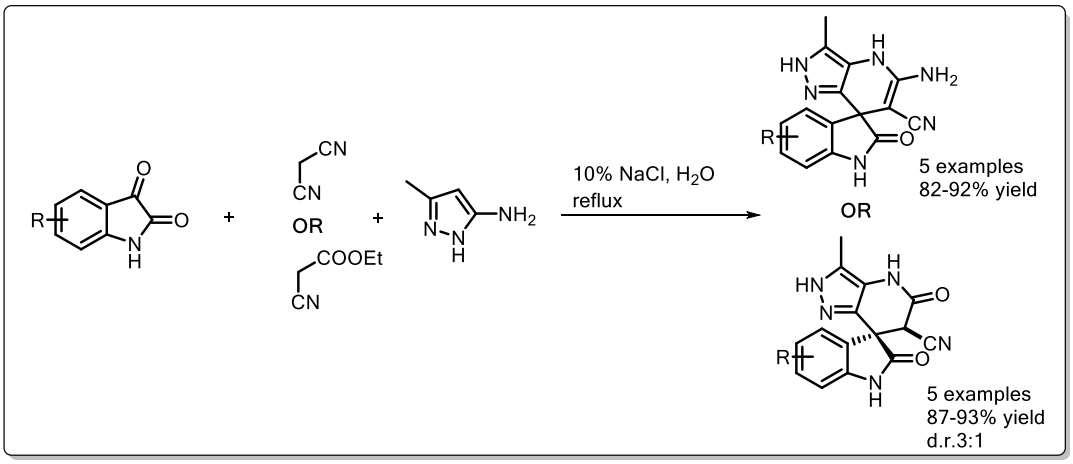
Scheme 1.2 Ugi reaction performed on-water for the synthesis of seleno cysteines (Wessjohann and coworkers)

MCR strategy was applied for the synthesis of highly functionalised thiophenes by Moghaddam and coworkers [45]. In this study 3-morpholino-3-thioxopropanenitrile was heated with α-haloketone and cyclohexyl isocyanide in water at 60 °C to yield the desired thiophenes in considerably moderate to good yields (59-74%) (**Scheme 1.3**).



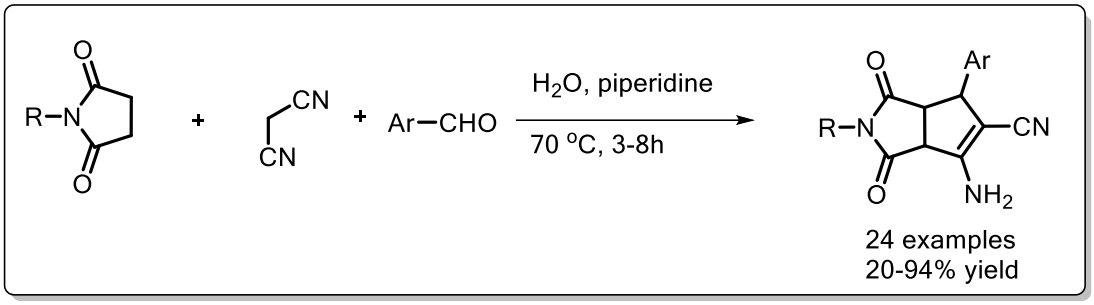
Scheme 1.3 On-water synthesis of highly functionalised thiophenes (Moghaddam and coworkers)

Dandia in 2012 reported the synthesis of spiroxindoles *via* a novel MCR route, where the reaction between isatin, malononitrile/ α-cyanoacetic ester and 5-amino-3-methylpyrazole was catalysed by sodium chloride in water to result in the formation of spiroxindoles in good to excellent yields (**Scheme 1.4**) [46]. The products obtained were a mixture of diastereomers in 3:1 ratio.



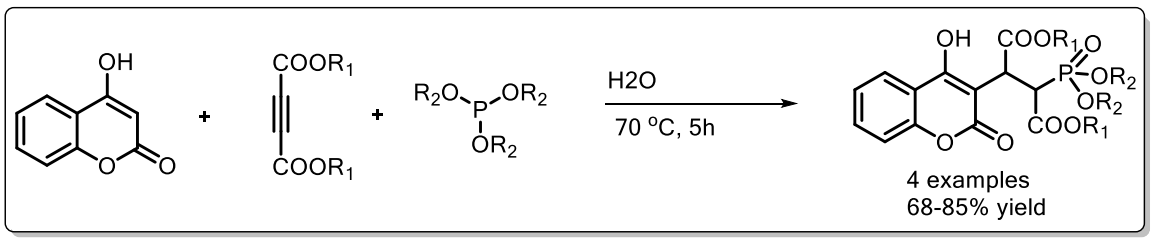
Scheme 1.4 NaCl catalysed, on-water, multicomponent synthesis of spiroxindoles (Dandia et al.)

In another instance, an on-water, piperidine catalysed reaction between hydantoin, aldehydes and malononitrile to result in the formation of 2-azapyrrolidines was reported by Vasuki and Rajarathinam (**Scheme 1.5**) [47]. The product formed was obtained as a single diastereomer in moderate to good yields.



Scheme 1.5 On-water, piperidine catalysed synthesis of 2-azapyrrolidines (Vasuki and Rajarathinam)

A multicomponent synthesis of phosphonates was reported by Rostami-Charati and Hossaini, where trialkylphosphites were treated with 4-hydroxycoumarin and activated acetylenes at 70 °C, on-water, to render the corresponding phosphonates in good yields (**Scheme 1.6**) [48].

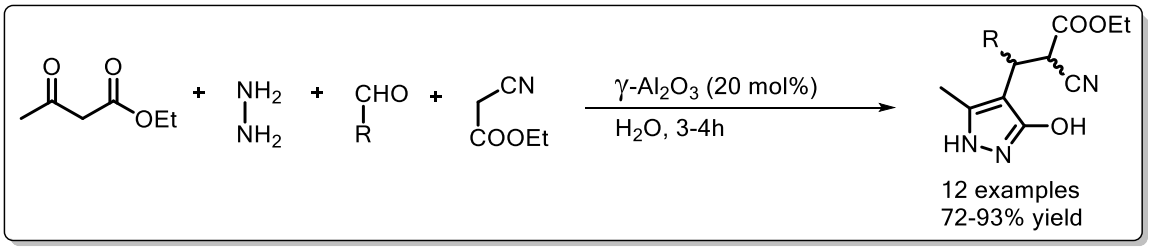


Scheme 1.6 Synthesis of phosphonate derivatives on-water (Rostami-Charati and Hossaini)

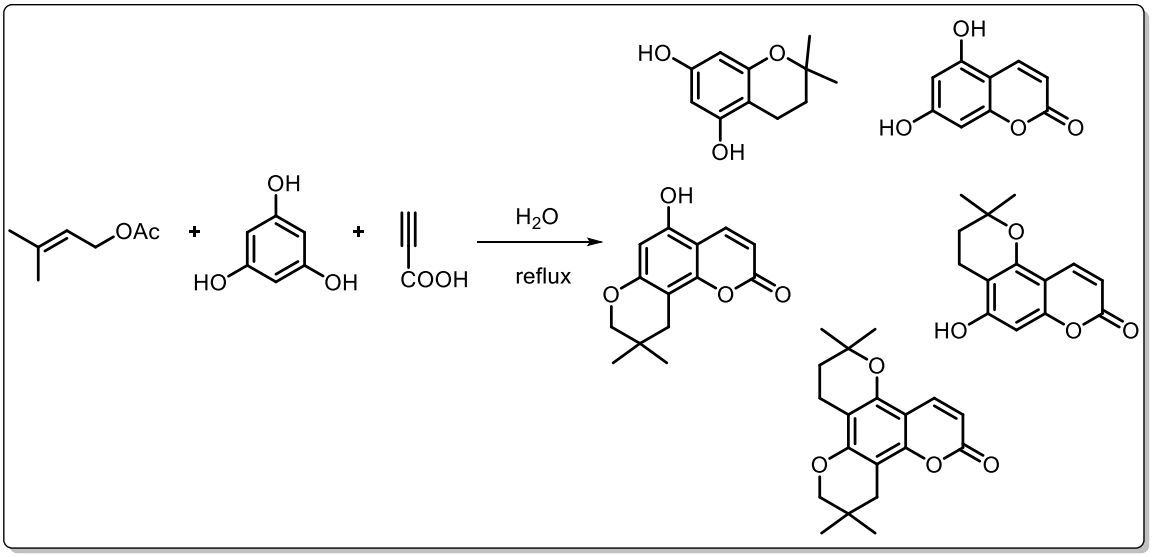
Following this Myrboh and coworkers reported a γ-alumina catalysed multicomponent synthesis of β-functionalised 5-methyl-1*H*-pyrazol-3-ol derivatives by reacting *in situ* generated 3-methyl-1*H*-pyrazol-5-ones (formed *via* the reaction between ethylacetoacetate and hydrazine) with aldehydes and ethylcyanoacetate in aqueous media. The corresponding pyrazol-3-ol derivatives

were obtained as a diastereomeric mixture in 1:1 ratio in good to excellent yields (**Scheme 1.7**) [49].

Qu and coworkers synthesised 5-methoxyseselin and alloxanthoxyletin skeletons by MCR approach on-water under catalyst free conditions and by only varying the molar ratios of the reactants namely isoprenyl acetate, propiolic acid and phloroglucinol (**Scheme 1.8**) [50].



Scheme 1.7 Synthesis of β-functionalised 5-methyl-1*H*-pyrazol-3-ol derivatives (Myrboh and coworkers)



Scheme 1.8 Catalyst free, on-water MCR approach towards the synthesis of 5-methoxyseselin and alloxanthoxyletin scaffolds (Qu and coworkers)

On-water reactions are often found to be associated with the claim that they are environmentally benign and thereby green. However, this fact does take a hit when we realise that environmental impact is not only determined by the solvent used. The efficacy of the reaction in terms of atom economy (which is almost

always achieved by MCRs), nature of the solvent used during the post reaction workup, the residual amount of organic compounds or catalysts or additives that remain in the aqueous waste and the cost of cleaning up or proper disposal also add up to the greenness factor [51-53]. The mere finding of a reaction that performs well in the presence of water gives very little information about the potential environmental impact.

c) Solventless MCRs

Moving from the perspective of green solvents, there is another perspective to performing reactions effectively under solventless conditions. It has risen up to be a lucrative and interesting yet challenging topic owing to the fact that absence of solvents would mean elimination of the process of generating solvent wastes. However, working under such conditions does complicate the process of mixing the reactants and also obstruct the course of the reaction. Nevertheless, many MCRs have been reported to be performed without the incorporation of a solvent [54, 55] and the techniques that have emerged to give the best results are mechanochemical process [56], MW irradiation [57] and infra-red (IR) irradiation [58].

We have seen that MCRs have run a long mile to prove its pivotal role in the development of modern chemistry. However, there are still some fertile lands to till and explore the scopes and limitations of MCRs. Moreover, with the advent of green chemistry, cleaner organic reactions performed under milder and energy efficient conditions and high selectivity will be the standards in near future. The existing methods will continue to develop and reform as newer methodologies are discovered. Development of analytical and computational techniques will also reduce the planning time and help researchers design highly selective protocols.

We have also seen that the newer MCRs work in lines of green chemistry and continue to evolve in that route. This will make MCRs a valuable asset for a synthetic chemist for developing spectrum of biologically active products and complexes which can revolutionise minor as well as industrial scale research.

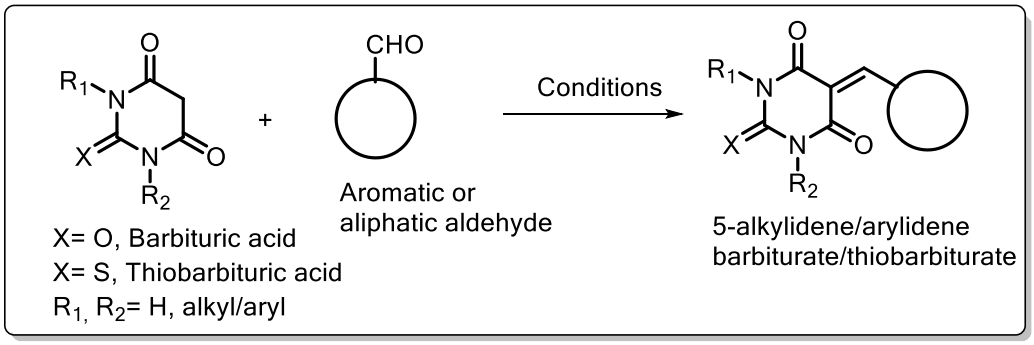
1.2 5-Arylidene/alkylidene barbiturates/thiobarbiturates

The chemistry of arylidene and alkylidene compounds has engaged a lot of researchers throughout the world and has brought to light intensive scientific studies focusing on the methods of preparation, reactivity and usage. They have been found to be pharmaceutically active on their own and also open a wide arena of application as a starting material or as an *in situ* formed intermediate. This class of compounds is usually prepared through Knoevenagel condensation of aldehyde and active methylene compounds *via* base [59], acid [60] or surfactant [61] catalysed methods. However, recent reports have also shown the formation of alkylidene/arylidene compounds under solvent free conditions and even in the absence of a catalyst [62, 63]. Knoevenagel condensations have also been reported to be carried out on solid supports promoted by IR [6] or MW [64, 65] irradiations, under solvent free conditions. Although there are a number of classes of alkylidene/arylidene compounds, we shall only discuss about the 5-alkylidene/arylidene derivatives of barbituric acid and thiobarbituric acid here.

1.2.1 Synthesis of 5-arylidene/alkylidene derivatives of barbituric and thiobarbituric acids

Medicinal chemists have been attracted to barbituric and thiobarbituric acids for over a century now [66, 67]. Their therapeutic values have earned them the spot of a go to component to be incorporated in several drug molecules bearing antibacterial, hypotensive and tranquilizing properties, which are still available in

the market [68]. They are used for the clinical treatment of neurological disorders [69]. This valuable member of the pyrimidine family has been the centre of applications as precursors to several heterocyclic compounds and as oxidising agents showing high selectivity [70, 71]. A very useful compound prepared from barbituric or thiobarbituric acid is 5-arylidene/alkylidene barbiturate. It is prepared *via* Knoevenagel reaction of barbituric acid with varied aldehydes under different conditions (**Scheme 1.9**).



Scheme 1.9 Synthesis of 5-alkylidene/arylidene barbiturates and thiobarbiturates

First reported to have been synthesised under reflux in water using acetic acid as a catalyst [72], the compound have come up with numerous methodologies of preparation. Villemin and Labiad reported the synthesis of 5-arylidenebarbiturates under the influence of MW irradiation in the presence of montmorillonite KSF clay [73]. On the other hand Dewan and Singh reported the use of various catalysts like ammonium acetate/acetic acid mixture, silica gel, basic alumina, sodium chloride, montmorillonite KSF and K-10 and KSF/NaCl for the synthesis of 5-arylidene barbiturate derivatives [74]. They even went to apply mechanochemical method for the purpose [75]. Solventless synthesis of the compound has been reported to be accomplished under IR and MW irradiation and in the presence of bismuth chloride [76-78]. Bismuth chloride catalysis in the presence of water for the synthesis of 5-arylidene barbiturates has been reported by Khan *et al.* [79].

Similar catalysis with ethanolamine and L-tyrosine has also been reported [80, 81].

1.2.2 Reactivity of 5-alkylidene/arylidenebarbiturates/thiobarbiturates

5-alkylidene/arylidene barbiturates and thiobarbiturates are electrophilic entities and participate in various conjugate addition and cycloaddition processes. Mayer and co-workers reported that 5-arylidene 1,3-dimethylbarbituric acid has a similar electrophilicity parameter, “E”, to 5-arylidene Meldrum’s acid which is further in line with the electrophilicity of benzylidenemalononitriles [82]. In fact, the barbiturate derivatives are much more potent electrophiles than the malonates. Again, while considering the thiobarbiturates, it was found to display higher electrophilicity than the barbiturates. This was attributed to the higher positive polarisation of the nitrogen atoms of thiobarbiturates than the barbiturates. The E values are shown in **figure 1.2** [83].

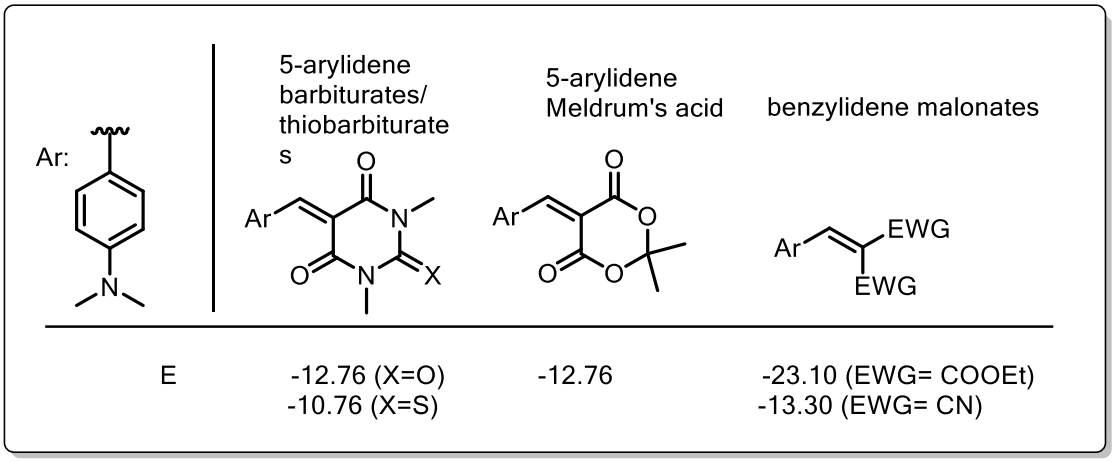
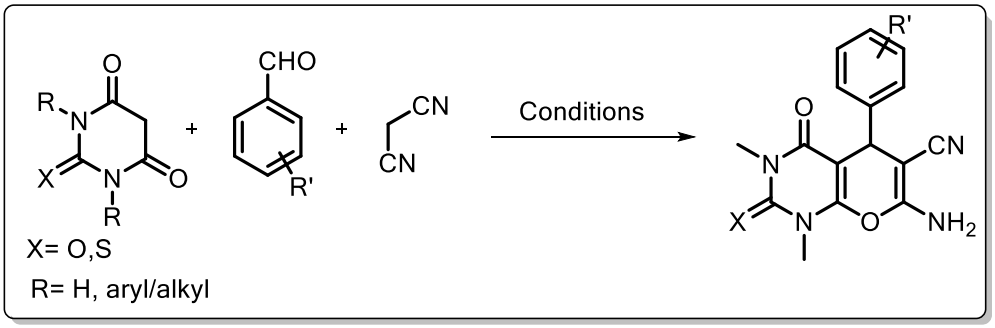


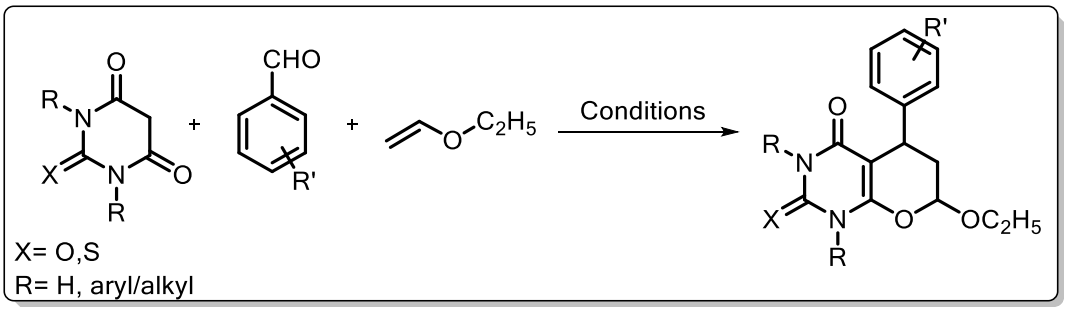
Figure 1.2 Comparison of the electrophilicity parameter (E) of various arylidene and benzylidene compounds

5-arylidene/alkylidene barbiturates have been explored for their electrophilicity and utilised for the synthesis of several spiro and fused heterocycles. In many a case as shown in **Scheme 1.10** and **Scheme 1.11** the 5-arylidene/alkylidene barbiturates are formed *in situ* to react with a third component present in the

reaction mixture and yield the desired products [84, 85]. They are excellent candidates for one-pot synthesis and hold up to the standards of green MCRs. In this thesis, the *in situ* formation of the 5-arylidene/alkylidene barbiturates and thiobarbiturates have been explored in each and every protocol developed and then further reacted with other reactants to explore the scope of cyclisation on-water. Some already reported protocols have been revisited to state the shortcomings of the existing routes and to establish new mechanistic approaches to them.



Scheme 1.10 Three component reaction for the synthesis of 1*H*-pyrano[2,3-*d*]pyrimidines *via* the formation of 5-arylidene barbiturate intermediate



Scheme 1.11 [4+2] cycloaddition between *in situ* formed 5-arylidene barbiturate and activated alkene for the synthesis of 2*H*-pyrano[2,3-*d*]pyrimidines

1.3 Objectives of the work

The ever increasing demand for bioactive heterocyclic compounds with naturally prevalent core units has instigated us to undertake a manifold objective into designing methodologies for the synthesis of pharmaceutically active/important

nitrogen and oxygen heterocycles. This will be accomplished majorly by the application of one-pot multicomponent reaction strategy which includes intramolecular cyclocondensation as a key step. Moreover, all the reaction routes designed will also involve the formation of 5-alkyl/arylidene barbiturate intermediates and will be carried out on-water. Accomplishing the said objective is not our only aim. We also intend to fulfill the following targets:

[1] To promote economical and environmentally friendly experimental procedures (green chemistry).

[2] To study the selectivity involved in the reactions.

[3] To accomplish the synthesis of an array of fused heterocycles and establish the possible synthetic pathways for the construction of basic skeleton of biologically potent scaffolds.

[4] To accomplish a comprehensive study of the scope and limitations of the cyclisation methodologies.

The methodologies developed, in the works reported in this thesis, have been laid on the grounds that have been either overlooked or generalized to be similar to some similar reported theories. Since 5-alkyl/arylidene barbiturate intermediates are not new to synthetic organic chemists, therefore developing newer methodologies which involved them required extensive literature survey. That is where the planning of the work begins. Subsequently, the following strategies were always kept under consideration while drawing out the rationale for the study:

[1] Whether the reaction could be carried out on-water or not?

[2] Whether the products could be isolated without chromatography?

[3] Whether previously prevalent issues with the synthesis of the scaffolds was addressed or not?

REFERENCES

[1] Ruijter, E., Scheffelaar, R., and Orru, R. V. Multicomponent reaction design in the quest for molecular complexity and diversity. *Angewandte Chemie International Edition*, 50(28):6234-6246, 2011.

[2] Dömling, A., Wang, W., and Wang, K. Chemistry and biology of multicomponent reactions. *Chemical Reviews*, 112(6):3083-3135, 2012.

[3] Sheehan, S.M., Masters, J.J., Wiley, M.R., Young, S.C., Liebeschuetz, J.W., Jones, S.D., Murray, C.W., Franciskovich, J.B., Engel, D.B., Weber II, W.W. and Marimuthu, J. A four component coupling strategy for the synthesis of D-phenylglycinamide-derived non-covalent factor Xa inhibitors. *Bioorganic and Medicinal Chemistry Letters*, 13(14):2255-2259, 2003.

[4] Cao, H., Liu, H., and Dömling, A. Efficient multicomponent reaction synthesis of the schistosomiasis drug praziquantel. *Chemistry–A European Journal*, 16(41):12296-12298, 2010.

[5] Richter, H. G., Benson, G. M., Blum, D., Chaput, E., Feng, S., Gardes, C., and Bleicher, K. H. Discovery of novel and orally active FXR agonists for the potential treatment of dyslipidemia and diabetes. *Bioorganic and Medicinal Chemistry Letters*, 21(1):191-194, 2011.

[6] Ishikawa, H., Suzuki, T., and Hayashi, Y. High-yielding synthesis of the anti-influenza neuramidase inhibitor (−)-oseltamivir by three “one-pot” operations. *Angewandte Chemie International Edition*, 121(7):1330-1333, 2009.

[7] Anastas, P., and Eghbali, N. Green chemistry: principles and practice. *Chemical Society Reviews*, 39(1):301-312, 2010.

[8] Trost, B. M. The atom economy—a search for synthetic efficiency. *Science*, 254(5037):1471-1477, 1991.

[9] Tietze, L. F. Domino reactions in organic synthesis. *Chemical Reviews*, 96(1):115-136, 1996.

[10] Strecker, A. Ueber die künstliche Bildung der Milchsäure und einen neuen, dem Glycocoll homologen Körper. *Justus Liebigs Annalen der Chemie*, 75(1):27-45, 1850.

[11] Hantzsch, A. Condensationsprodukte aus Aldehydammoniak und ketonartigen Verbindungen. *Berichte der Deutschen Chemischen Gesellschaft*, 14(2):1637-1638, 1881.

[12] Ma, Z., Ma, Z., and Zhang, D. Synthesis of multi-substituted pyrrole derivatives through [3+2] cycloaddition with tosylmethyl isocyanides (TosMICs) and electron-deficient compounds. *Molecules*, 23(10):2666, 2018.

[13] Biginelli, P. Ueber aldehyduramide des acetessigäthers. *Berichte der Deutschen Chemischen Gesellschaft*, 24(1):1317-1319, 1891.

[14] Singh, S. B. Copper nanocatalysis in multi-component reactions: A green to greener approach. *Current Catalysis*, 7(2):80-88, 2018.

[15] Robinson, R. LXIII.—A synthesis of tropinone. *Journal of the Chemical Society Transactions*, 111:762-768, 1917.

[16] Passerini, M. Isonitriles. II. Compounds with aldehydes or with ketones and monobasic organic acids. *Gazzetta Chimica Italiana*, 51:181-189, 1921.

[17] Elders, N., Ruijter, E., de Kanter, F. J., Groen, M. B., and Orru, R. V. Selective formation of 2-imidazolines and 2-substituted oxazoles by using a three-component reaction. *Chemistry–A European Journal*, 14(16):4961-4973, 2008.

[18] MacMillan, D. W. The advent and development of organocatalysis. *Nature*, 455(7211):304-308, 2008.

[19] Galema, S. A. Microwave chemistry. *Chemical Society Reviews*, 26(3):233-238, 1997.

[20] Doraiswamy, L. K., and Thompson, L. H. Sonochemistry: science and engineering. *Industrial and Engineering Chemical Research*, 38:1215-1249, 1999.

[21] Tietze, L. F., and Lieb, M. E. Domino reactions for library synthesis of small molecules in combinatorial chemistry. *Current Opinion in Chemical Biology*, 2(3):363-371, 1998.

[22] Kappe, C. O. The generation of dihydropyrimidine libraries utilizing Biginelli multicomponent chemistry. *QSAR and Combinatorial Science*, 22(6):630-645, 2003.

[23] Noguez, M. O., Marcelino, V., Rodríguez, H., Martín, O., Martínez, J. O., Arroyo, G. A., and Miranda, R. Infrared assisted production of 3,4-dihydro-2 (1 H)-pyridones in solvent-free conditions. *International Journal of Molecular Sciences*, 12(4):2641-2649, 2011.

[24] Anastas, P. T., and Kirchhoff, M. M. Origins, current status and future challenges of green chemistry. *Accounts of Chemical Research*, 35(9):686-694, 2002.

[25] Gu, Y. Multicomponent reactions in unconventional solvents: state of the art. *Green Chemistry*, 14(8):2091-2128, 2012.

[26] Earle, M. J., and Seddon, K. R. Ionic liquids. Green solvents for the future. *Pure and Applied Chemistry*, 72(7):1391-1398, 2000.

[27] Isambert, N., Duque, M. D. M. S., Plaquevent, J. C., Genisson, Y., Rodriguez, J., and Constantieux, T. Multicomponent reactions and ionic liquids: a perfect synergy for eco-compatible heterocyclic synthesis. *Chemical Society Reviews*, 40(3):1347-1357, 2011.

[28] Paprocki, D., Madej, A., Koszelewski, D., Brodzka, A., and Ostaszewski, R. Multicomponent reactions accelerated by aqueous micelles. *Frontiers in Chemistry*, 6:502, 2018.

[29] Chanda, A., and Fokin, V. V. Organic synthesis “on-water”. *Chemical Reviews*, 109(2):725-748, 2009.

[30] Wohler, F. Ueber kunstliche bildung des harnstoffs. *Annual Review of Physical Chemistry*, 37:330-333, 1828.

[31] Baeyer, A., and Drewsen, V. Darstellung von indigblau aus orthonitrobenzaldehyd. *Berichte der Deutschen Chemischen Gesellschaft*, 15(2):2856-2864, 1882.

[32] Head-Gordon, T., and Hura, G. Water structure from scattering experiments and simulation. *Chemical Reviews*, 102(8):2651-2670, 2002.

[33] Li, C. J., and Chan, T. H. *Organic Reactions in Aqueous Media*. Sussex, Unined Kingdom, Wiley, 1997.

[34] Grieco, P. A. (Ed.). *Organic Synthesis in Water*. Springer Science and Business Media, London, 1997.

[35] Itami, K., and Yoshida, J. I. The use of hydrophilic groups in aqueous organic reactions. *The Chemical Record*, 2(4):213-224, 2002.

[36] Brogan, A. P., Dickerson, T. J., and Janda, K. D. Enamine-based aldol organocatalysis in water: are they really “all wet”? *Angewandte Chemie International Edition*, 118(48):8278-8280, 2006.

[37] Hayashi, Y., Sumiya, T., Takahashi, J., Gotoh, H., Urushima, T., and Shoji, M. Highly diastereo- and enantioselective direct aldol reactions in water. *Angewandte Chemie International Edition*, 45(6):958-961, 2006.

[38] Lipshutz, B. H., Aguinaldo, G. T., Ghorai, S., and Voigtritter, K. Olefin cross-metathesis reactions at room temperature using the nonionic amphiphile “PTS”: just add water. *Organic Letters*, 10(7): 1325-1328, 2008.

[39] Lipshutz, B. H., Ghorai, S., and Aguinaldo, G. T. Ring-Closing Metathesis at Room Temperature within Nanometer Micelles using Water as the Only Solvent. *Advanced Synthesis and Catalysis*, 350(7-8):953-956, 2008.

[40] Lipshutz, B. H., and Abela, A. R. (). Micellar catalysis of Suzuki− Miyaura cross-couplings with heteroaromatics in water. *Organic Letters*, 10(23): 5329-5332, 2008.

[41] Huisgen, R. 1,3-dipolar cycloadditions. Past and future. *Angewandte Chemie International Edition*, 2(10): 565-598, 1963.

[42] Huisgen, R., and Padwa, A. 1,3-Dipolar cycloaddition chemistry. *Wiley, New York*, 1(2):55-92, 1984.

[43] Pirrung, M. C., and Sarma, K. D. Aqueous medium effects on multi-component reactions. *Tetrahedron*, 61(48):11456-11472, 2005.

[44] Abbas, M., Bethke, J., and Wessjohann, L. A. One pot synthesis of selenocysteine containing peptoid libraries by Ugi multicomponent reactions in water. *Chemical Communications*, 5:541-543, 2006.

[45] Moghaddam, F. M., Bardajee, G. R., and Dolabi, M. An efficient one-pot synthesis of tri-substituted thiophenes *via* a multicomponent reaction in water. *Journal of Sulfur Chemistry*, 31(5):387-393, 2010.

[46] Dandia, A., kumar Laxkar, A., and Singh, R. New multicomponent domino reaction on-water: highly diastereoselective synthesis of spiro [indoline-3, 4′-

pyrazolo [3,4-*b*] pyridines] catalyzed by NaCl. *Tetrahedron Letters*, 53(24):3012-3017, 2012.

[47] Rajarathinam, B., and Vasuki, G. Diastereoselective multicomponent reaction in water: synthesis of 2-azapyrrolizidine alkaloid analogues. *Organic Letters*, 14(20):5204-5206, 2012.

[48] Rostami-Charati, F., and Hossaini, Z. Facile synthesis of phosphonates via catalyst-free multicomponent reactions in water. *Synlett*, 23(16):2397-2399, 2012.

[49] Rohman, M. R., Mecadon, H., Khan, A. T., and Myrboh, B. Synthesis of important β-functionalized 5-methyl-1*H*-pyrazol-3-ol derivatives in the presence of γ-alumina catalyst in aqueous medium. *Tetrahedron Letters*, *53(39):*5261-5264, 2012.

[50] Cao, J. L., Shen, S. L., Yang, P., and Qu, J. A catalyst-free one-pot construction of skeletons of 5-methoxyseselin and alloxanthoxyletin in water. *Organic Letters*, 15(15):3856-3859, 2013.

[51] Trost, B. M. Atom economy-a challenge for organic synthesis: homogeneous catalysis leads the way. *Angewandte Chemie International Edition*, 34(3):259-281, 1995.

[52] Blackmond, D. G., Armstrong, A., Coombe, V., and Wells, A. Water in organocatalytic processes: debunking the myths. *Angewandte Chemie International Edition*, 46(21):3798-3800, 2007.

[53] Wei, W., Keh, C. C. K., Li, C. J., and Varma, R. S. Clean Tech. Environ. *Policy*, 7:62, 2005.

[54] Singh, M. S., and Chowdhury, S. Recent developments in solvent-free multicomponent reactions: a perfect synergy for eco-compatible organic synthesis. *RSC Advances*, 2(11):4547-4592, 2012.

[55] Attanasi, O. A., Favi, G., Mantellini, F., Moscatelli, G., and Santeusanio, S. Synthesis of functionalized pyrroles via catalyst-and solvent-free sequential three-component enamine− azoene annulation. *The Journal of Organic Chemistry*, 76(8):2860-2866, 2011.

[56] Pascu, M., Ruggi, A., Scopelliti, R., and Severin, K. Synthesis of borasiloxane-based macrocycles by multicomponent condensation reactions in solution or in a ball mill. *Chemical Communications*, 49(1):45-47, 2013.

[57] Cui, S. L., Lin, X. F., and Wang, Y. G. Parallel synthesis of strongly fluorescent polysubstituted 2, 6-dicyanoanilines via microwave-promoted multicomponent reaction. *The Journal of Organic Chemistry*, 70(7):2866-2869, 2005.

[58] Flores-Conde, M. I., Reyes, L., Herrera, R., Rios, H., Vazquez, M. A., Miranda, R., and Delgado, F. Highly regio-and stereoselective Diels-Alder cycloadditions via two-step and multicomponent reactions promoted by infrared irradiation under solvent-free conditions. *International Journal of Molecular Sciences*, 13(3):2590-2617, 2012.

[59] Choudary, B. M., Kantam, M. L., Kavita, B., Reddy, C. V., and Figueras, F. Catalytic C–C bond formation promoted by Mg–Al–O–t-Bu hydrotalcite. *Tetrahedron*, 56(47):9357-9364, 2000.

[60] Prajapati, D., Lekhok, K. C., Sandhu, J. S., and Ghosh, A. C. Magnesium per chlorate as efficient lewis acid for the knoevenagel condensation between β-diketones and aldehydes. *Journal of the Chemical Society, Perkin Transactions*, 1:959, 1996.

[61] Khan, R. H., Mathur, R. K., and Ghosh, A. C. Tellurium (IV) tetrachloride catalysed facile Knoevenagel reaction. *Synthetic Communications*, 26(4):683-686, 1996.

[62] Tanaka, K. *Solvent-free organic synthesis*. John Wiley and Sons, New York, 2009.

[63] Tanaka, K., and Toda, F. Solvent-free organic synthesis. *Chemical Reviews*, 100(3):1025-1074, 2000.

[64] Obrador, E., Castro, M., Tamaríz, J., Zepeda, G., RenéMiranda, and Delgado, F. Knoevenagel condensation in heterogeneous phase catalyzed by IR radiation and tonsil actisil FF. *Synthetic Communications*, 28(24):4649-4663, 1998.

[65] Balalaie, S., and Nemati, N. One-pot preparation of coumarins by Knoevenagel condensation in solvent-free condition under microwave irradiation. *Heterocyclic Communications*, 7(1):67-72, 2001.

[66] Bojarski, J. T., Mokrosz, J. L., Bartoń, H. J., and Paluchowska, M. H. Recent progress in barbituric acid chemistry. *Advances in Heterocyclic Chemistry*, *38*:229-297, 1985.

[67] Tietze, L. F., and Bärtels, C. Inter-and intramolecular hetero-Diels-Alder reactions, 32. Iridoids, 26. Synthesis of bridged homoiridoids from secologanin by tandem-Knoevenagel-hetero-Diels-Alder reactions. *Liebigs Annalen der Chemie*, 1991(2):155-160, 1991.

[68] Khan, K. M., Khan, M., Khan, A., Perveen, S., Naz, F., and Iqbal Choudhary, M. 5-Arylidene *N,N'*-dimethylbarbiturates as Urease Inhibitors. *Journal of the Chemical Society of Pakistan*, 36(3):45-51, 2014.

[69] Smith, M. C., and Riskin, B. J. The clinical use of barbiturates in neurological disorders. *Drugs*, 42(3):365-378, 1991.

[70] Charles, W., Schroeder, C. H., and Paul, L. K. U.S. Patent No. 3,097,213. Washington, DC: U.S. Patent and Trademark Office, 1963.

[71] Tanaka, K., Chen, X., Kimura, T., and Yoneda, F. Oxidation of thiol by 5-arylidene 1,3-dimethylbarbituric acid and its application to synthesis of unsymmetrical disulfide. *Tetrahedron Letters*, 28(36):4173-4176, 1987.

[72] D'yachkov, A. I., Ivin, B. A., Smorygo, N. A., and Sochilin, E. G. Studies of pyrimidines. XXVII. Condensation of 2-thiobarbituric acid with benzaldehydes. Composition and structure of reaction products in some solvents. *Chemischer Informationsdienst*, 7(37):625-628, 1976.

[73] Villemin, D., and Labiad, B. Clay catalysis: dry condensation of barbituric acid with aldehydes under microwave irradiation. *Synthetic Communications*, 20(21):3333-3337, 1990.

[74] Dewan, S. K., and Singh, R. One pot synthesis of barbiturates on reaction of barbituric acid with aldehydes under microwave irradiation using a variety of catalysts. *Synthetic Communications*, 33(17):3081-3084, 2003.

[75] Wang, X. S., Shi, D. Q., and Tu, S. J. Synthesis of 3-aryl-3-(5, 5-dimethyl-3-hydroxyl-cyclohex-2-ene-1-one-2-yl)-propionamide derivatives catalyzed by KF/Al_2O_3. *Chinese Journal of Organic Chemistry*, 22(11):909-912, 2002.

[76] Alcerreca, G., Sanabria, R., Miranda, R., Arroyo, G., Tamariz, J., and Delgado, F. Preparation of benzylidene barbituric acids promoted by infrared irradiation in absence of solvent. *Synthetic Communications*, 30(7):1295-1301, 2000.

[77] Khalafinezhad, A., and Hashemi, A. Microwave enhanced knoevenagel condensation of barbituric acid with aromatic aldehydes on basic alumina, *Iranian Journal of Chemistry and Chemical Engineering,* 2001:9-11, 2001.

[78] Prajapati, D., and Sandhu, J. S. Bismuth (III) chloride as a New Catalyst for Knoevenagel Condensation in the Absence of Solvent. *Chemistry Letters*, 1992(10):1945-1946, 1992.

[79] Khan, K. M. An improved method for the synthesis of 5-arylidene barbiturates using $BiCl_3$. *Journal of the Chemical Society of Pakistan*, 31(6):823, 2010.

[80] Bamanie, F. H. A., Shehata, A. S., Moustafa, M. A., and Mashaly, M. M. Green chemistry 1: simple and efficient synthesis in water and antibacterial activity of 5-arylidene derivatives of thiobarbituric and barbituric acids. *J. American Science*, 8(1):481-485, 2012.

[81] Thirupathi, G., Venkatanarayana, M., Dubey, P. K., and Bharathi Kumari, Y. Facile and green syntheses of 5-arylidene-pyrimidine-2,4,6-triones and 5-arylidene-2-thioxo-dihydro-pyrimidine-4,6-diones using L-tyrosine as an efficient and eco-friendly catalyst in aqueous medium. *Chemical Science Transactions*, 2:441-446, 2013.

[82] Seeliger, F., Berger, S. T., Remennikov, G. Y., Polborn, K., and Mayr, H. Electrophilicity of 5-benzylidene-1,3-dimethylbarbituric and-thiobarbituric acids. *The Journal of Organic Chemistry*, 72(24):9170-9180, 2007.

[83] Pałasz, A. Synthesis of fused uracils: pyrano [2,3-*d*] pyrimidines and 1,4-*bis* (pyrano [2,3-*d*] pyrimidinyl) benzenes by domino Knoevenagel/Diels-Alder reactions. *Monatshefte für Chemie-Chemical Monthly*, 143:1175-1185, 2012.