Chapter 1

Introduction and review of literature

1.1. General introduction

1.1a. Scope of heterocyclic compounds

Heterocycles are organic compounds containing at least one hetero atom (N, O, S, and P) in the carbocyclic ring and represent the largest classical division in the field of organic chemistry [1]. They are either aromatic or non-aromatic compounds. The non-aromatic heterocyclic compounds are considered as the cyclic analogues of acyclic amines, ethers, amides, esters, thio-ethers etc. Their properties depend on the ring strains which are commonly built up of 3-7 membered ring systems. These compounds are widely distributed as natural products in the form of alkaloids, pyrimidines, purines, oxazines, acridines etc., and also active component of biomolecules such as DNA and RNA, chlorophyll and hemoglobin [2-3]. They have broad range of biological, material and industrial importance and also to the functioning of any developed human society as well. Most of them have been frequently found as a key structural unit in synthetic pharmaceuticals and agrochemicals. The majority of pharmaceutical products that mimic natural products with biological activity include antidepressant, antitumor, antibiotic, anti-inflammatory, antimalarial, antidiabetic, antibacterial, anti-HIV, antifungal, antimicrobial, antiviral, fungicidal, herbicidal, and insecticidal agents [4-8]. Thus, it becomes a potent area for the synthetic and medicinal chemists to design and developed better pharmaceuticals, pesticides, insecticides, rodenticides, and weed killers by following the natural models. More than 67% of the compounds listed in Comprehensive Medicinal Chemistry (CMC) database are aromatic and nonaromatic heterocycles [9-10]. Further potential uses of these compounds include in material science as dyestuff, fluorescent materials, brightening agents, information storage, analytical reagents and polymeric material [11-12]. A large number of industries based on cosmetics, reprography, plastics, solvents, antioxidants, and vulcanization accelerators use these compounds as additives and modifiers for various purposes. Some of them have been utilized to synthesize organometallic compounds [13-14].

The 5-6 membered N- or O- heterocycles are of exceptional interest in the pharmaceutical industry, as they appear in the core structure of several drugs molecules (**Fig.1**) [15-16]. Besides these core units of O- or N-heterocycles, some natural products have the basic framework of both O- and N- atoms containing carbocyclic rings such as oxazine, oxazoline, oxazole etc. (**Fig.1**) [17-18]. Therefore, organic chemist has paid considerable attention to design heterocycles by developing new and efficient synthetic methodologies.

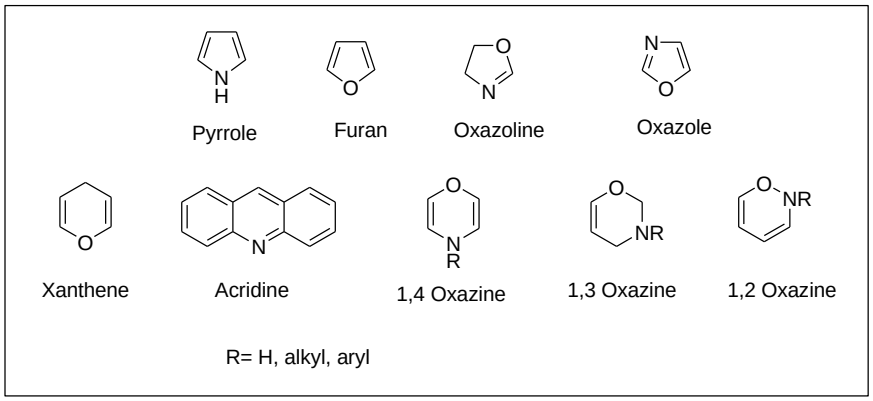


Fig.1: N and O containing heterocycles

1.1b. Natural acridine, xanthene and naphthoxazine heterocycles

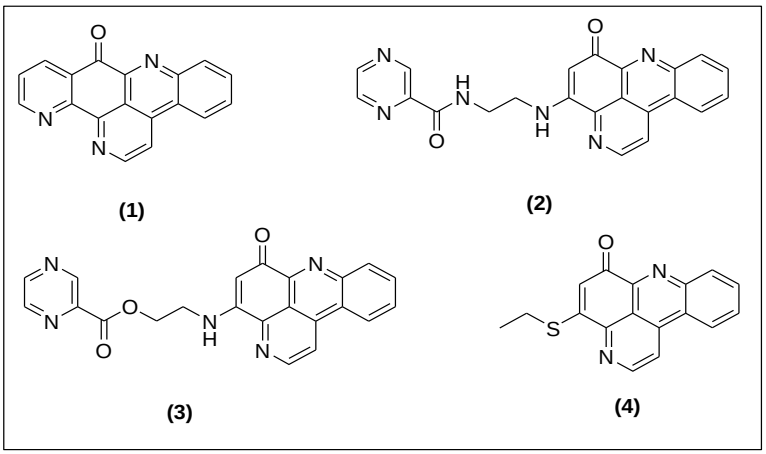


Fig. 2: Natural pyridoacridine alkaloids

The physical and chemical properties of each hetero compound depend on the nature of heteroatom, size and degree of unsaturation of the rings and also the positions of the heteroatom. It was reported that natural product bearing pyridoacridine unit belong to the class of alkaloid and exhibit strong anti-tuberculosis activity [19]. Some examples of such type of natural products are ascididemin (**1**), N-(2-(6-oxo-6H-pyrido[2,3,4-kl]acridin-4-ylamino)ethyl)pyrazine-2-carboxamide **(2)**, 2-(6-oxo-6H-pyrido[2,3,4-kl]acridin-4-ylamino)ethyl pyrazine-2-carboxylate **(3)** and 4-(ethylthio)-6H-pyrido[2,3,4-kl]acridin-6-one (**4)** which have strong potential to inhibit the growth of mycobacterium tuberculosis (MTB) with little cytotoxicity (**Fig.2**) [20-21].

Another class of natural products with acridine skeleton such as asulacrine, amsacrine and N-(2-(dimethylamino)ethyl)acridine-4-carboxamide (DACA) possess anticancer activity and can also be synthesized in laboratory (**Fig.3**) [22-23].

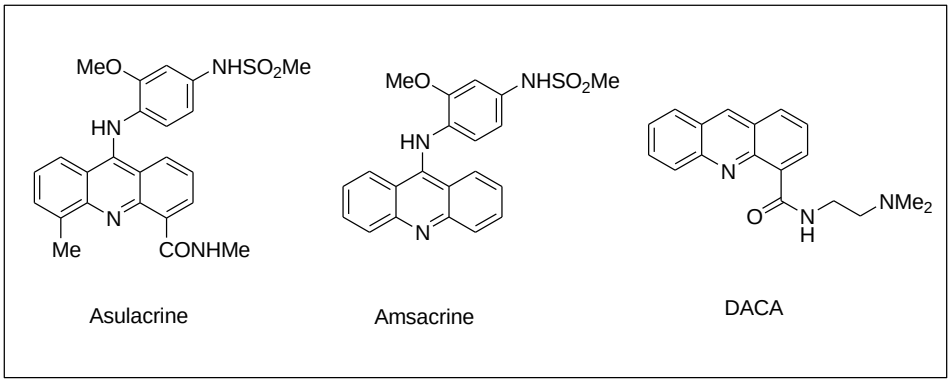


Fig.3: Acridine derivatives with anticancer activity

The first natural halogenated xanthene is 9-hydroxy-10-methoxy-2-methyl-8*H*-furo[2,3-a]xanthen-8-one which was isolated from a Chinese medicinal plant Blumeariparia (B1) DC, that prevented the growth of liver cancer cell Bel-7404 at MIC 25 microgram/L (**Fig.4**) [24]. The xanthone unit (3,4,4a,9-tetrahydro-2*H*-xanthen-9-one) of secalonic acid is a typical natural product (**Fig.4**). The presence of tetrahydroxanthone unit is also observed in lactone ergochrisin, eumitrin pigments, beticolin toxins and antibiotic xanthoquinodin A1 [25-26].

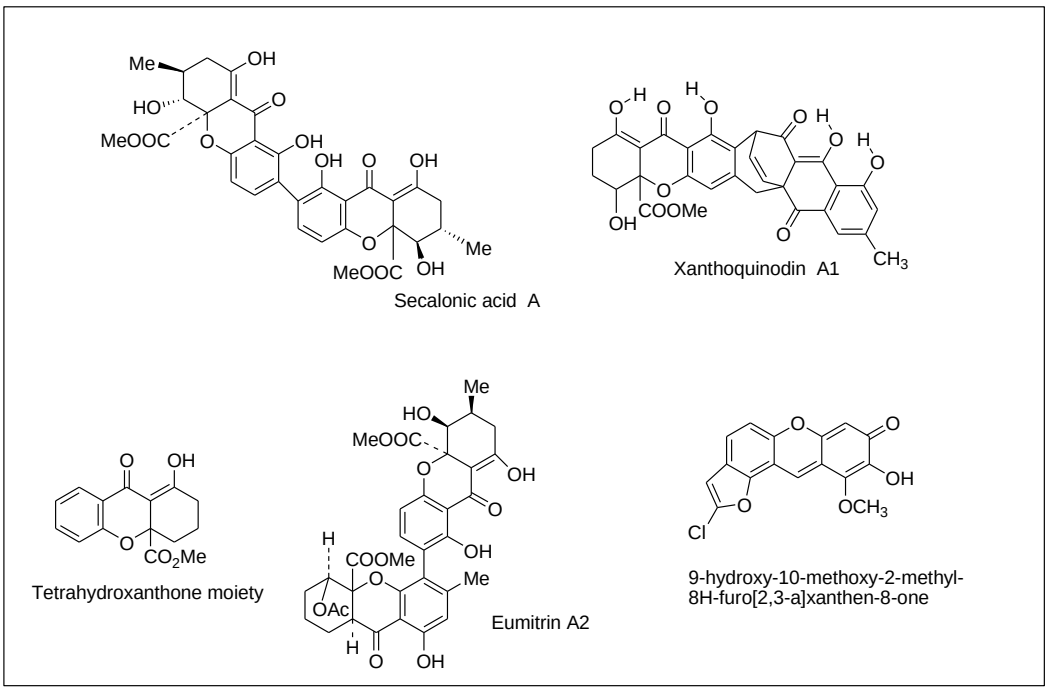


Fig. 4: Natural xanthenes

Natural 1,2-oxazine FR 900482 and its dihydro derivatives FR 66979 isolated from *Streptomyces sandaensis* No. 6897 showed promising antitumor activity. Modified derivatives FK 973 and FK 317 of FR 900482 oxazines also have strong antitumor activity

and they are structurally related to mytomycin C, a compound used in cancer therapy [27-28] (**Fig.5**).

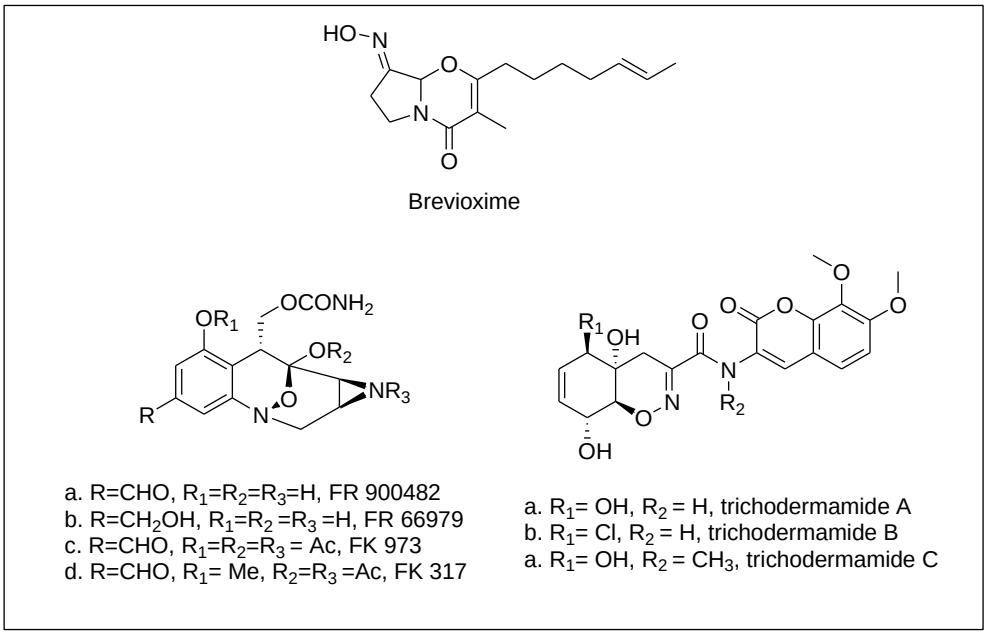


Fig.5: Natural oxazines

Trichodermamides A and B, two natural 1, 2 oxazines isolated as secondary metabolites from marine derived fungal strains, Trichoderma virens CNL910 and CNK266 (**Fig.5**). Trichodermamide B displayed significant in vitro cytotoxicity against HCT-116 human colon carcinoma with IC_{50} of 0. 32 µg/mL while trichodermamide A showed only weak cytotoxicity against HL 60 cell line with an IC_{50} of 38. 5 µg /mL [29]. Another derivative trichodermamide C obtained from a culture broth of the endophytic fungus *Eupenicllium*sp also exhibited similar activity with IC_{50} of 0. 68 µg /mL [30-31].

The 1,3-oxazine unit also found in Brevioxime which was isolated from *Penicilliumbrevicompactum* possessing very high activity as juvenile hormone biosynthesis inhibitor (**Fig.5**) [32].

1.1c. Pharmacological significance of acridine, xanthene and oxazine derivatives

Acridines and their fused derivatives are known to possess various pharmacological activities**,** including anticancer, antitumor, antiviral, antimicrobial, antimalarial, analgesic and anti-inflammatory, which stimulate synthesis and further studies of new compounds of this series (**Fig.6a**) [33-37]. In 1917, Ehrlich and Benda *et al* discovered the antimicrobial property of acridine [38]. During the World War II, the discovery of quinacrine or mepacrine as antimalarial drug was observed in place of quinine [39]. At

present, a number of acridine based medicines are marketed for various clinical purposes (**Fig**.**6b**). For example, proflavin (3,6-diaminoacridine) acts as topical antibacterial and antifungal agent [40]. Likewise pyronaridine and acranil have been used as antimalarial drugs which destroy the sexual erythrocytic forms of plasmodia [41]. Nitracrine [1-nitro-9-(dimethyl-aminopropylamino)acridine] is also utilized for the treatment of mammary and ovarian tumors [42].

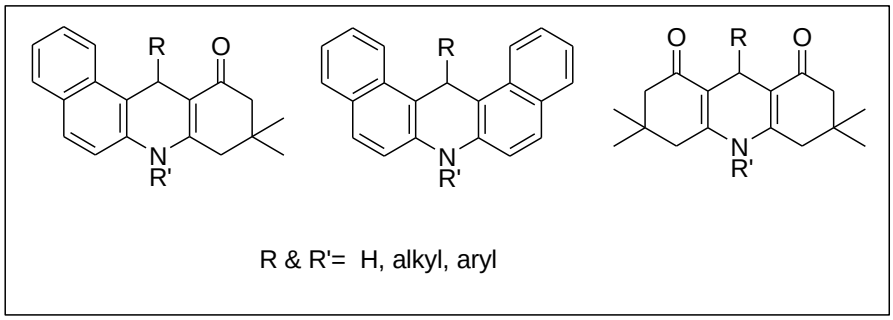


Fig.6a: Acridine derivatives

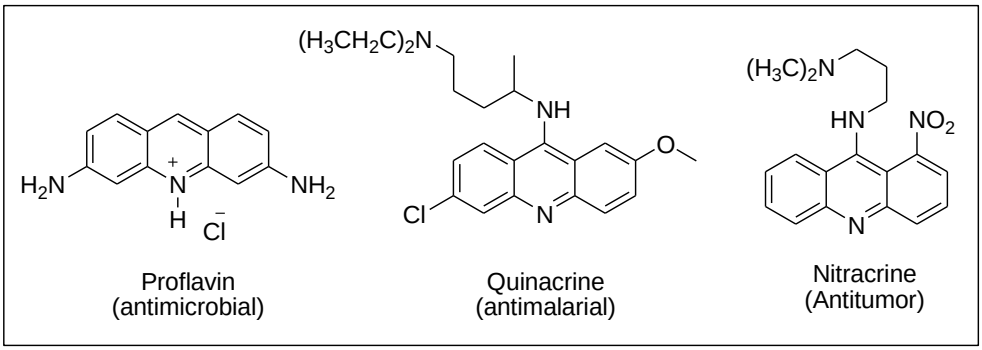


Fig.**6b**: Some acridine derivatives in clinical uses

Polyhydroacridines and polyhydroacridinones are multifunctionalized 1,4-dihydropyridines (DHPs) derivatives. These are well known compounds because of their wide pharmacological profiles [43-44]. The variations of different substituents or heteroatoms on the DHP unit have extended their studies on the structure - activity relationship in the molecular interactions at the receptor level [45-46]. The acridinedione derivatives also investigated for their potential as laser dyes**,** photochemical/physical properties**,** electrochemical properties**,** and interactions with DNA [47-50]**.** Another important derivative of acridine is polyhydrodibenzoacrdines which have characteristic luminescent properties and at the same time, only limited numbers of studies are available in literature for the synthesis as well as biological activity [51-52].

The synthesis of xanthenes especially benzoxanthenes has emerged as a powerful tool in organic synthesis because of their extensive biological and therapeutic properties such as antibacterial, antivirals and anti-inflammatory agents as well as efficiency in photodynamic therapy and antagonists for the paralyzing action of zoxazolamine (**Fig.6c**) [53-57]. These compounds are used as leuco-dye in laser technologies and in pH sensitive fluorescence materials for visualization of biomolecules [58-59]. The biological study of xanthone derivatives in *Hypericum* species revealed strong and selective inhibition of MAO-A, in vitro toxicity, in vivo antitumor activity along with other antiviral and antibacterial activities [60-61].

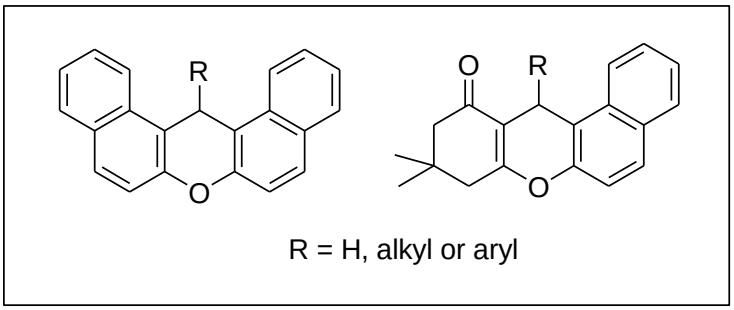


Fig.6c: Xanthene derivatives

Oxazines are named as [1,2], [1,3] and [1,4] derivatives depending on the relative positions of oxygen and nitrogen atoms in the carbocyclic ring (**Fig.1**) [62]. Substituted 1, 3-oxazines are ubiquitous in various natural products, and many of them have been recognized as pivotal intermediate for the synthesis of molecules with various medicinal properties [63-64]. The structurally diverse oxazine derivatives have been reported as analgesic, anti-tubercular, anticancer, anti-HIV, antihypertensive, antithrombotic and antiulcer activities [65-69]. Particularly, naphthoxazine derivatives possess therapeutic potential for the treatment of Parkinson's disease [70-71]. Other fused 1, 3-oxazine systems include pyrrolo/pyrido [2,1-a] benzoxazin-one [72], pyrido[2,3-e][1, 3]oxazine [73], benzoxazine derivatives [74] substituted imidazo [2,1-b][1,3]oxazines derivatives [75-76] which also have the similar potential to exhibit wide pharmacological activities (**Fig.6d**).

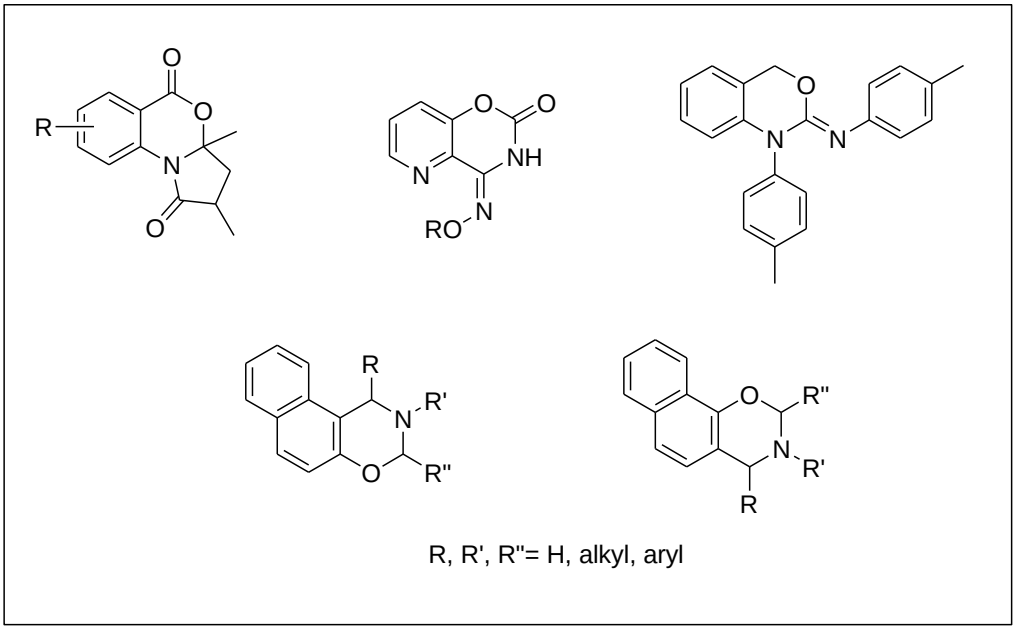


Fig.6d: Fused 1, 3-oxazine derivatives

1.2. General methodologies for the preparation of acridine, xanthene and naphthoxazine derivatives

Nowadays, synthetic chemists are concerned with regard to the tight legislation on the maintenance of 'greenness' in synthetic strategies and processes which strongly influences on the use of "greener" reaction condition in synthetic chemistry [77-80]. The rising health and environmental hazards from volatile organic compounds (VOC) in chemical processes have become an important issue for environmental pollution because recovery efficiency is far from satisfactory. In concern with the environmental effects from volatile substrates, organic chemists prefer to perform reactions either avoiding solvents or using alternate non-flammable, non-toxic, non-volatile and inexpensive "greener solvents'' such as ionic liquids, water, super critical fluids etc. as these reduce the burden of solvent disposal and also enhance the rate of many organic reactions [81-83]. The combination of acid catalyzed one-pot multicomponent /multistep approach in greener medium will develop sustainable chemical methods having less reaction time, more product selectivity, mild reaction conditions, possibility to form various products and simple work-up process [84-86]. This section covers the review of different common methodologies used for studying the synthesis of title compounds in different chapters of the thesis.

1.2a. Solvent-free organic synthesis

The earlier belief that no reaction occurs in absence of solvent, is no valid in chemistry at present position of sustainable development process [87-90]. In organic synthesis, the major problem comes from the volatile solvents and thus has a detrimental effect on individual health and atmosphere by air pollution. Solvent-free syntheses are found to be superior in various aspects over those carried out in solution phase which can be pointed out in the following manner [90-92].

- There is no reaction medium or solvent to collect, purify, and recycle.
- Commonly, the products don't require any extensive purification methods.
- Sequential solvent-free reactions are possible in high yielding systems.
- The reactions are often rapid, sometimes reaching substantial completion in several minutes as compared to hour with organic solvents.
- Energy usage may be significantly lower.
- Functional group protection-deprotection can be avoided.
- Making solvent-free protocols not only more environmentally benign but also more economically feasible.

The word "neat'' is more appropriate to give better description of solvent-free reaction of liquid substrates in absence of external solvent to remove confusion in many cases [93]. Solid phase synthesis and solid state reactions can also be considered as solvent-free reactions. Rothenberg *et al* [94] defined solid phase synthesis is the reaction of molecules from a fluid phase with a solid substrate without any solvent, e.g. solid phase peptide synthesis. In solid state reactions, direct interaction of macroscopic solid substrates form the solid product without intervention of a liquid or vapour phase. Sometimes solid state reactions can also be performed using the substrate alone or introducing them on an inert solid support such as silica, alumina, clay or other matrices [94-96]. It has been observed that the solid phase synthesis clearly involve the formation of a liquid phase such as aldol condensation and Baeyer–Villager oxidations, oxidative coupling of naphthols using iron chloride, condensation of amines and aldehydes to form azomethines, homo-etherification of benzylic alcohols using p-toluenesulfonic acid [87-88, 92]

1.2b. One-pot protocol of organic reactions

At present time scientific community is in search of technique of synthesis which has minimal impact on environment and human health. In this regard the most potential sustainable approach is the one-pot syntheses starting from two component or multicomponent reactions [97-99]. It avoids the isolation of unstable reaction intermediates in various steps and increases the rate of reaction to yield the selective product along with other advantages such as simple operation, high yields and formation of fewer side products. Multicomponent reactions (MCRs) are defined as chemical syntheses involving at least three or more components of different types [100]. Thus one-pot MCRs has gained significant importance as a tool for the synthesis of a wide variety of useful compounds including pharmaceuticals for their environmental advantages and cost effectiveness in organic synthesis. The conventional multiple step synthesis of any organic compound involves a numbers of steps including extraction and purification which results in huge amount of waste and also inefficiency of the procedure [101-104]. Unlike this conventional method, these multicomponent reactions require less time, form high yield of product and always give single or target product and thereby it reduces the use of energy and man power. In addition, the solvent used is very less and makes the synthetic protocol more efficient [104-107]. As sustainable development approach, one-pot MCRs are very useful methodologies for the synthesis with high level of molecular diversity and complexity and also to generate molecular library of chemical compound that possesses medicinal and other biological properties and have contribution towards society. Therefore, the developments of novel multicomponent strategies have attracted synthetic organic chemist to a great extent in the field of drug discovery, organic synthesis, and material science [107-110].

1.2c. Organic synthesis in water medium

From the last two decades, Green Chemistry has attained the status of a major scientific discipline which prefers the utilization of “safer solvent” in chemical reactions. It is well known that solvent always plays an integral part in any synthetic process. Most of the volatile organic solvents, that are used repeatedly in different synthetic and manufacturing processes are poisonous and very harmful and have negative impact towards environment and society [85, 90, 93].

From literature, it has been seen that water acts as unconventional greener solvent in organic reactions and maximizes the synthetic efficiency by stabilizing the catalyst,

changing the reaction selectivity or facilitating product isolation [111-114]. Earlier it was not considered as suitable solvent for organic synthesis because of the insolubility of organic molecules and incompatibility of the intermediates in water. In 1983, Breslow [115] and Grieco [116-117] explored the efficiency of water as reaction medium in increasing rate and selectivity of Diels-Alder reactions which started a new path for organic synthesis. As reaction medium water has several advantages including its cost, safety and simple operation. Sometimes, water provides mild reaction condition, less reaction time and increases the product selectivity. Both homogeneous and heterogeneous catalysts can be reused in aqueous solution [91, 118-120]. Tedious protection and deprotection steps can also be avoided, particularly in carbohydrate, nucleoside or peptide chemistry. In view of sustainable properties of aqueous medium, many new one-pot MCRs have been successfully developed in water as reaction medium instead of conventional organic solvents [121-123]. Hydrophobic effects become prominent among non-polar molecules in aqueous solution as compared to organic solvents and these determine the selectivity of synthetic strategies in the desired direction by aggregation of hydrophobic regions of the reactants [124-127]. The lower solubility of organic substrates in water medium can easily overcome by using organic co-solvents, ionic derivatization, surfactants or hydrophilic auxiliaries.

1.2d. Uses of acid catalytic systems in one-pot organic synthesis

Catalysis is the fundamental pillars of green sustainable chemistry for design of chemical products and processes that reduce generation of waste material and eliminate the uses of hazardous substances [128-129]. The design of new catalysts and study of their catalytic activity in petrochemical, chemical and pharmaceutical industries are simultaneously achieving the dual goals of environmental protection and economic benefit. Catalysis provides a path of changing the rate at which chemical bonds are formed and broken and of controlling the yields of chemical reactions to increase the amounts of desirable products from these reactions and reduce the amount of side products. The most challenging work for catalysis sciences is to understand how to design catalysts structures to control catalytic activity and selectivity. Many organic reactions are highly performed through one-pot, tandem, and domino or cascade reactions as these processes improve atom economy [85, 130-131]. Acid catalyzed multicomponent reaction is also an example of such type of approach where desired product can be prepared in a single vessel without

separation of any catalyst and reaction intermediates, which is already discussed earlier. Again multistep strategies are utilized for the production of fine and pharmaceutical chemicals which generate waste materials to the environment that also include various toxic and corrosive non-reusable acid catalysts. Several types of Brønsted or Lewis acids are widely used as catalyst in various organic transformations [132-133]. The direct use of liquid acids such as H_2SO_4, HCl, H_3PO_4 etc. are not favourable due to vigorous reaction condition, corrosive nature, toxicity, and hygroscopic nature, difficulty in separation, recovery and recycling [134]. In organic solvents, sometime homogeneous catalysed reactions create problem during separation of product from the catalyst and also exert corrosive effect on the reaction vessel. But this type of homogeneous catalysts can be recycled for several times in unusual solvents like water, ionic liquids, polyethylene glycol and supercritical fluids etc. [135-136]. One alternative of traditional acid catalysed organic reactions is the use of dual-solvent catalyst system of task specific acidic ionic liquids [137-138]. Heterogenization of Brønsted/Lewis acid catalysts on inert supports like silica, alumina, clay and polymer is also equally effective to make the process cleaner [139-141]. The direct use of solid acids as heterogeneous catalysts are observed to be more efficient to increase the rate of reaction at mild condition and thus reduce the reaction time in solution or in absence of solvent. Some of the significant features of the heterogeneous catalysts are [84-85]:

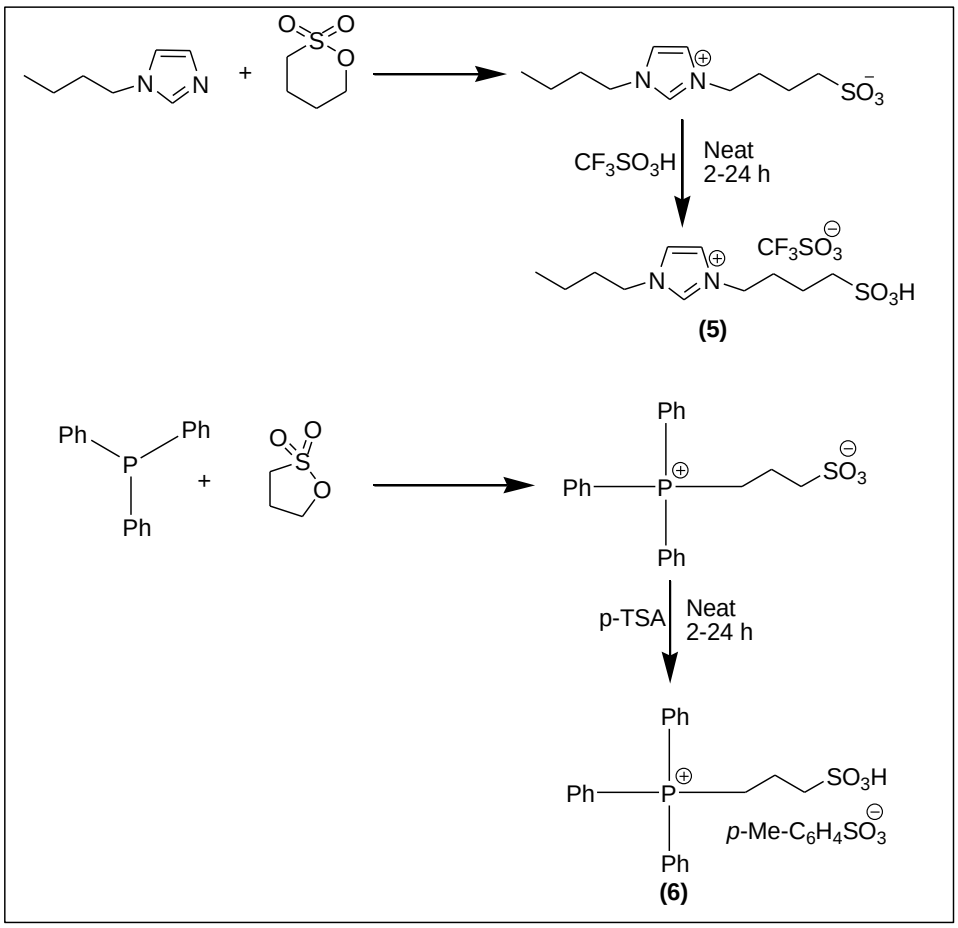
- They can be easily removed from reaction mixture by simple filtration.
- Excess catalyst can be used to drive reactions to completion without introducing difficulties in purification.
- Recycling of recovered catalyst is economical, environmentally-sound, and efficient.
- Ease of handling is especially important when dealing with expensive or time-intensive catalysts which can be incorporated into flow reactors and automated processes.
- Finely tune chemical properties by altering choice of support and its preparation.
- Toxic, explosive, and corrosive acids are often more safely handled when contained on solid support.
- Reactant on solid-support react differently, mostly more selectively, than their unbound counterparts.

As safer alternative of VOCs and dipolar aprotic solvents, synthetic chemists have developed ionic liquids as catalyst or reaction medium for organic reactions which are non-volatile. Ionic liquids (ILs) can easily defined as liquid electrolytes composed entirely of ions, and occasionally a melting point criterion has been proposed to distinguish between molten salts and ionic liquids (mp<100 °C). However, both molten salts and ionic liquids are better described as liquid compounds that display ionic-covalent crystalline structures [142-144]. Over the last two decades ionic liquids have gained major importance in the field of greener organic synthesis. It is also to mention that ILs was initially considered as alternative green reaction media because of their unique chemical and physical properties. But in present time they have crossed this boundary and showing their significant interest in controlling chemical reactions as solvent or catalyst [137-138, 145]. Their characteristics features include almost no vapor pressure, non-flammability, non-combustibility, high thermal stability, relatively low viscosity, wide window of temperature range for being liquids, and high ionic conductivity. They can easily be synthesized in research laboratory and reused for numbers of times. Furthermore, they offer favorable properties of homogeneous reactions by dissolving both polar and non-polar substrate and make the isolation of product easier in immiscible organic solvents [146-149]. By attaching various functional groups, ionic liquids have been synthesized for specific purpose as dual-solvent systems of acidic, basic and neutral as per requirement of the reaction [150-151]. In this thesis, we have developed new task specific acidic ILs and successfully applied for the preparation of one-pot synthesis of acidine, xanthene and naphthoxazine derivatives.

1.3. Reported methods for the synthesis of -SO_3H functionalized ionic liquid systems

From the beginning of 21st century ionic liquids containing specific functional group have received increasing interest from the synthetic chemist for their wide range of potential uses which can be achieved by varying the functionality of cation and anion [8]. Particularly, the addition of one or more -SO_3H group in cationic component of IL facilitates variation of physical properties of ILs like acidity, thermal stability and moisture stability depending on the nature of anionic part and thus makes them to applicable as catalysts or solvent in organic synthesis [152].

The initial attempt for the synthesis of sulfonic acid functionalized IL was made by Cole *et al* (2002) where his group synthesized imidazolium (**5)** and triphenylphosphinium (**6)** based ionic liquids by reaction of N-butyl imidazole or triphenyl phosphine with 1, 4-butane or 1, 4-propane sultone, respectively in DMF for 3 days at room temperature stirring. The IL (**5)** was viscous liquid while **(6)** was stiff glass type material liquefied at 80 °C (**Scheme-1**). Both ILs were screened as solvent/catalyst for Fischer esterification, alcohol dehydrodimerization and the pinacol/benzopinacole rearrangement reactions [153].



Scheme-1: Synthestic route of -SO_3H-functionalized ILs reported by Cole *et al*

The use of IL (**6**) as reusable catalyst for Fischer esterification of acetic acid and ethanol was investigated by Kristin and his co-worker in 2004 [154].

In 2004 Gu *et al* [155] reported the use of 1-(4-sulfonic acid)butyl-3-alkylimidazolium triflate **(7a-b) (Fig.7)** as reusable solvent and catalyst for the oligomerization of olefins in absence of other acid catalysts. They prepared these ILs using the same procedure as described by Cole *et al* [153].

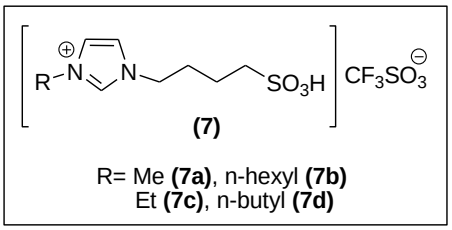


Fig.7: Structure of 1-(4-sulfonic acid)butyl-3-alkylimidazolium triflate

They also mentioned the synthesis of two more additional members of the above IL series (**7c-d)** in another literature and used for the esterification of aliphatic acid with olefin (**Fig. 7)** [156].

One more application of the 1-(4-sulfonic acid)butyl-3-methylimidazolium triflate (**7a)** IL as reusable catalyst was performed for the one-pot synthesis of α-aminophosphonates by Akbari *et al* in 2009 [157].

In the same year Gui *et al* (2004) [152] synthesized three halogen-free task specific Brønsted acidic ILs (**Fig.8**) such as 1-(4-sulfonic acid) butyl-3-methylimidazolium hydrogen sulfate **(8a)**, 1-(4-sulfonic acid) butylpyridinium hydrogen sulfate (**8b)** and N-(4-sulfonic acid) butyltriethylammonium hydrogen sulfate **(8c)** and applied them as catalyst for the esterification of ethanol by acetic acid.

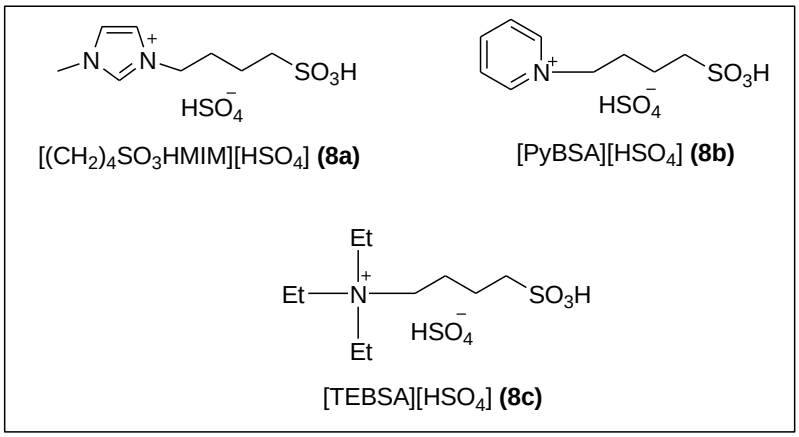


Fig.8: Structure of Brønsted acidic ILs containing $–SO_3H$

Xing *et al* in 2005 and 2007 [158-159] developed four water-stable Brønsted-acidic task-specific ionic liquids (TSILs) (**9)** by mixing equimolar mixture of different Brønsted acids (HBF_4, *p*-toluene sulfonic acid, H_2SO_4, H_3PO_4) with N-propane sulfone pyridinium (PSPy) at 40-80 °C within the time frame of 24 hour (**Fig.9**). The Brønsted acidities of

these pyridinium based sulfonic acid-functionalized ionic liquids (SFILs) were investigated by the Hammett function values.

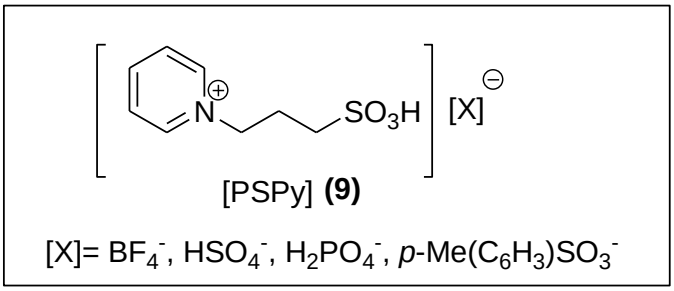
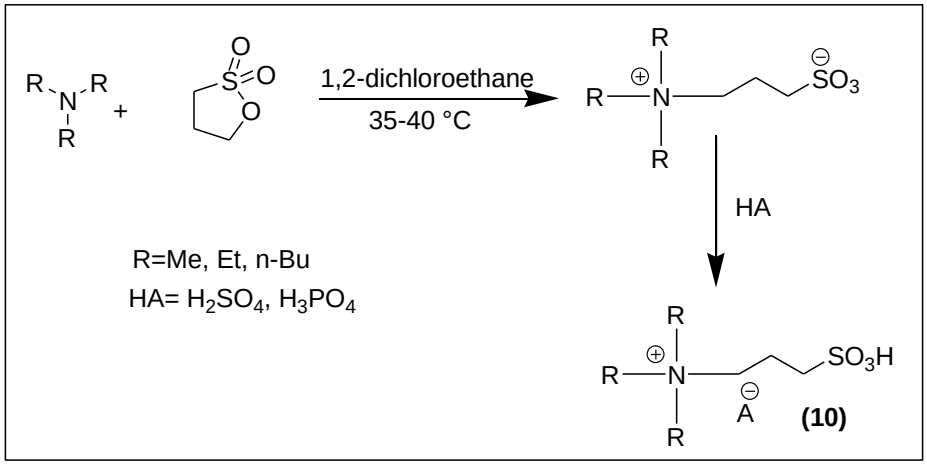


Fig.9: Sulfonic acid-functionalized pyridinium based ILs

In 2006 Fang *et al* [160] employed some -SO_3H group containing Brønsted acidic ILs (BAILs) (**10**) as dual reusable solvent-catalysts system for Fischer esterification reaction. They prepared these ILs in two step reactions through the formation of trialkylammonium-propane-sulfonates at 35-40 °C under nitrogen atmosphere during 24 h followed by reaction with equimolar amount of Brønsted acid (e. g. H_2SO_4, H_3PO_4) solution at room temperature stirring for 24 h at 40-80 °C (**Scheme-2).**



Scheme-2: Synthesis of trialkylammonium-propane-sulfonates based ILs

Several imidazolium based -SO_3H-functionalized ILs (**Fig.10**) was prepared by Li *et al* (2007) and examined them in the synthesis of dioctyl phthalate. The stability and reusability of these ILs were observed and it was found that 1-methyl-3-(3-sulfopropyl)-imidazolium hydrogen sulfate as the best catalyst under the optimized condition [161].

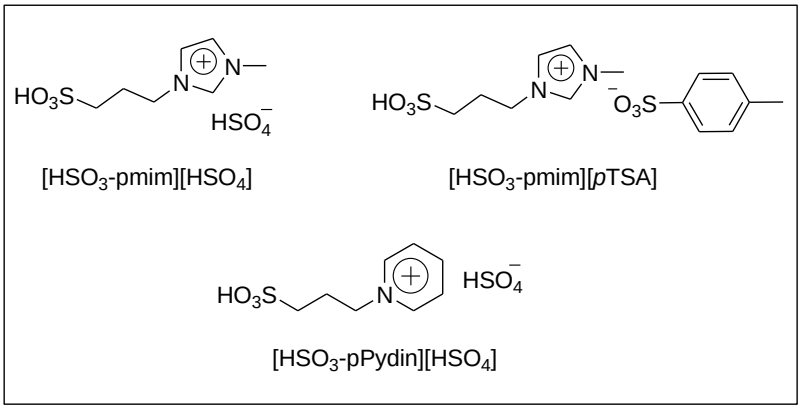
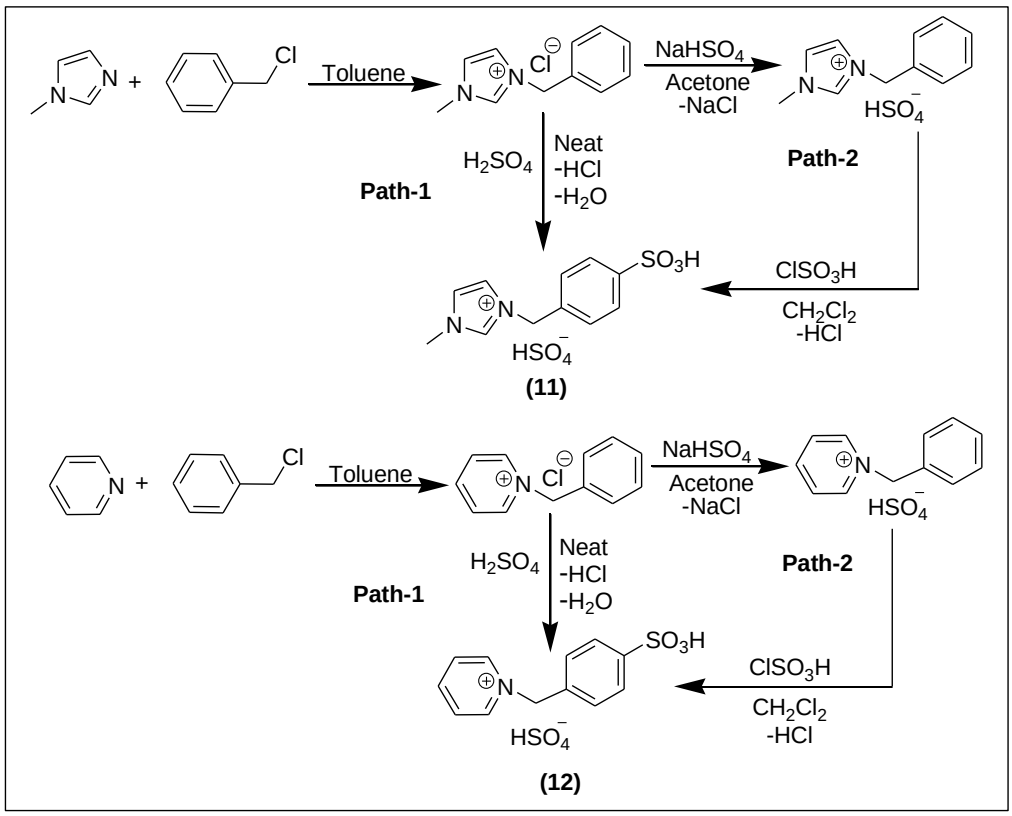


Fig.10: Ionic liquids synthesized by Li *et al*

Eli and his co-worker (2008) used two recyclable Brønsted acidic ionic liquids (**11** & **12**) that bear an aromatic sulfonic acid group on the imidazolium or pyridinium cation for Fischer esterification of long chain aliphatic acids with methanol and ethanol. Both ILs were prepared in two different routes (path-1 and path-2) in reaction **Scheme-3** [162]**.**



Scheme-3: Synthetic route of Brønsted acidic ionic liquids **(11)** and **(12)**

In 2008, Dai and his group designed two sulfonic acid functionalized benzimidazolium ILs 1-ethyl-3-(3-sulfopropyl)-benzimidazoliumtetrafluoroborate [PSebim][BF_4] (**13a)** and 1-ethyl-3-(3-sulfopropyl)-benzimidazolium hydrogen sulfate [PSebim][HSO_4] **(13b)**

(Fig.11) along with other type of acidic ILs. The preparation procedure involved with the formation of 1-ethylbenzimidazole from the vigorous reaction of benzimidazole and tetrabutyl ammonium bromide in 30% aqueous NaOH solution followed by dropwise addition of bromoethane and further heating at 45 °C for 12h. Reaction of sulfuric acid/tetrafluoroboric acid with aqueous solution of 1-ethylbenzimidazole at 90 °C for 2 h produced the corresponding ILs **(13a** and **13b**) in solid state. Among these ILs [PSebim][HSO_4] was utilized as reusable catalyst in acetalization of aromatic aldehydes with dilos [163].

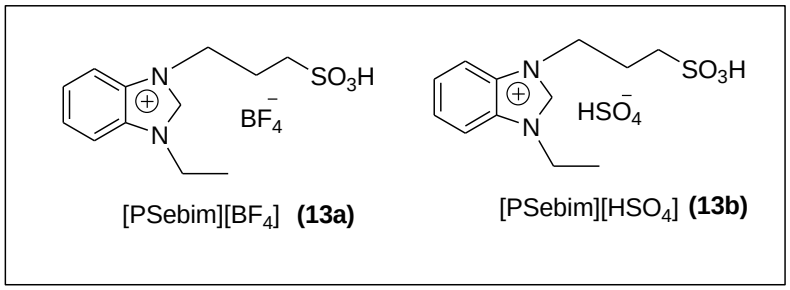


Fig.11: Structure of [PSebim][BF_4] and [PSebim][HSO_4]

Cheng *et al* (2008) prepared three N-(4-hydroxsulfonylbutyl) pyridinium based task-specific acidic ILs **(14a-c)** [BSPy][HSO_4], [BSPy][TfO] and [BSPy][pTSA] by following the method of Cole *et al* [153] and investigated their catalytic activity for the nitration of aromatic compounds with NO_2/air under solvent-free method (**Fig.12**). These ILs were well separated from the product and reused up to the fifth cycle [164].

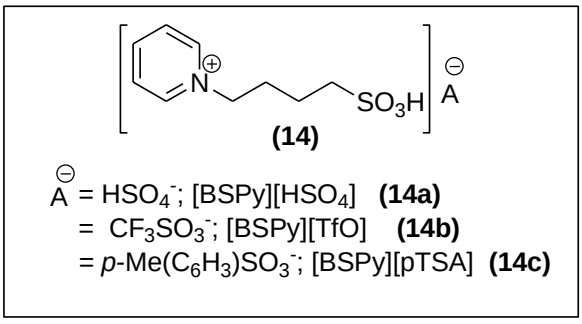
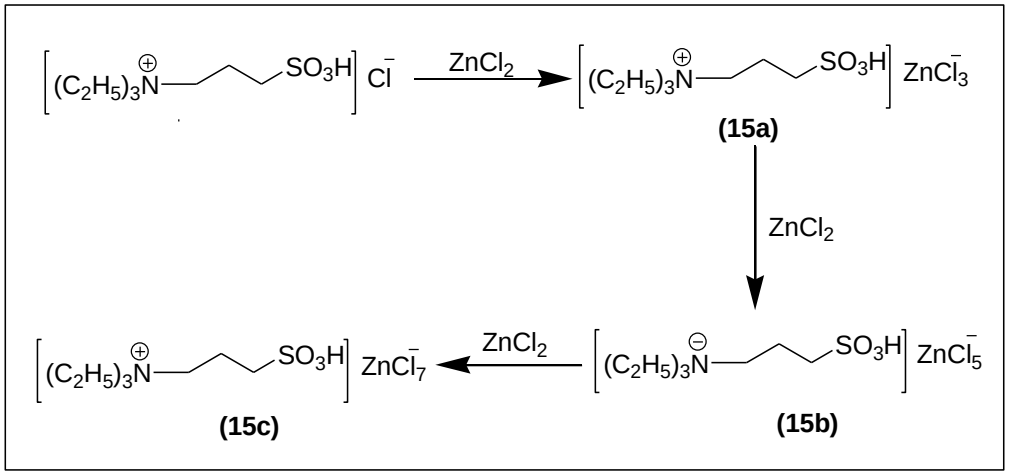


Fig.12: Structure of pyridinium based task specific acidic ILs

Three different types of Brønsted-Lewis acidic ILs of (3-sulfonic acid)-propyltriethylammonium chlorozincinates (**15a-c**) were prepared by Liu *et al* in 2008 by vigorous stirring a mixture of different mol fraction (mol fraction of $ZnCl_2$ = 0.5, 0.64, and 0.75) of zinc chloride with [HSO_3– $(CH_2)_3$–NEt_3][Cl] at 100 °C for 4 h and studied their catalytic activity for the dimerization of rosin (**Scheme-4**) [165].



Scheme-4: Synthesis of chlorozincinates containing Brønsted-Lewis acidic ILs

Yu and his group (2009) synthesized two sulfonic acid functionalized imidazolium based Brønsted acidic ionic liquid having perfluoroalkyl tails (**16a)** and (**16b)** shows in **Fig.13** and successfully utilised as Brønsted acid-surfactant combined catalyst for the multicomponent synthesis of 9, 10-diaryl-1,8-dioxo-decahydroacridine derivatives [166].

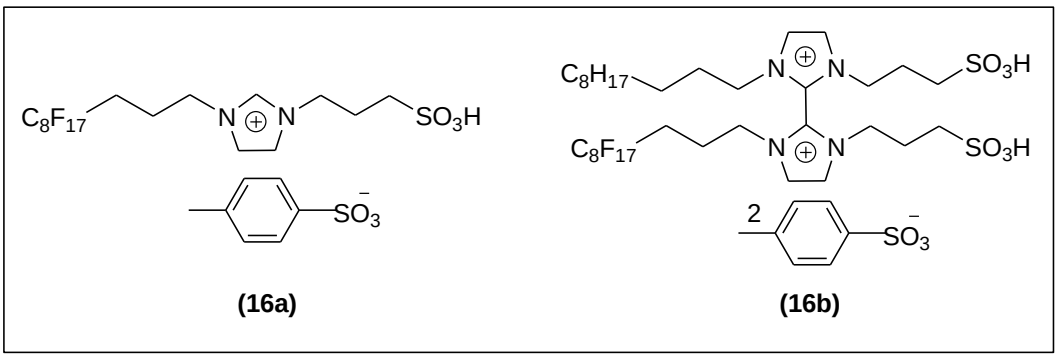


Fig.13: Brønsted acidic imidazolium based ionic liquid containing perfluoroalkyl tails

Peng and his co-worker in 2009 utilized several imidazolium and pyridinium based acidic ILs bearing –SO_3H (**17a-f** and **14b, Fig.14)** as reusable catalyst for the esterification of aliphatic acids with alcohols. They prepared these acidic ionic liquids (**17a-f**) from the reaction of zwitterions of 1-methylimidazole and 1, 4-butane sultone with different Brønsted acids (such as sulfuric acid, phosphoric acid, *p*-toluenesulfuric acid etc.) at 80 °C for 6 hour [167].

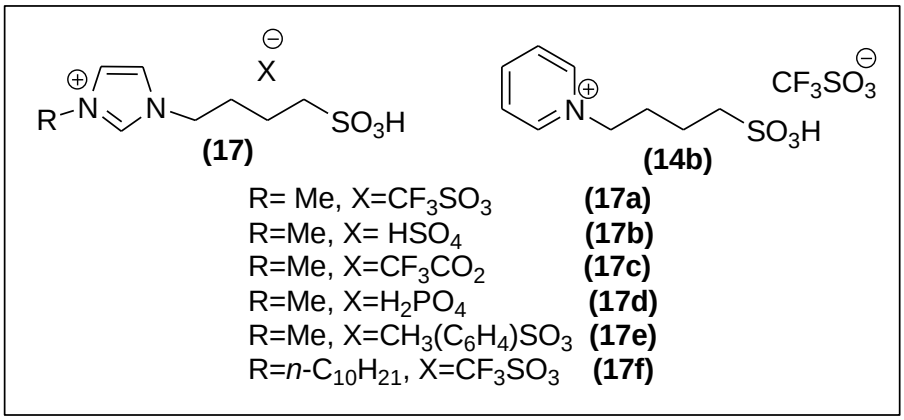
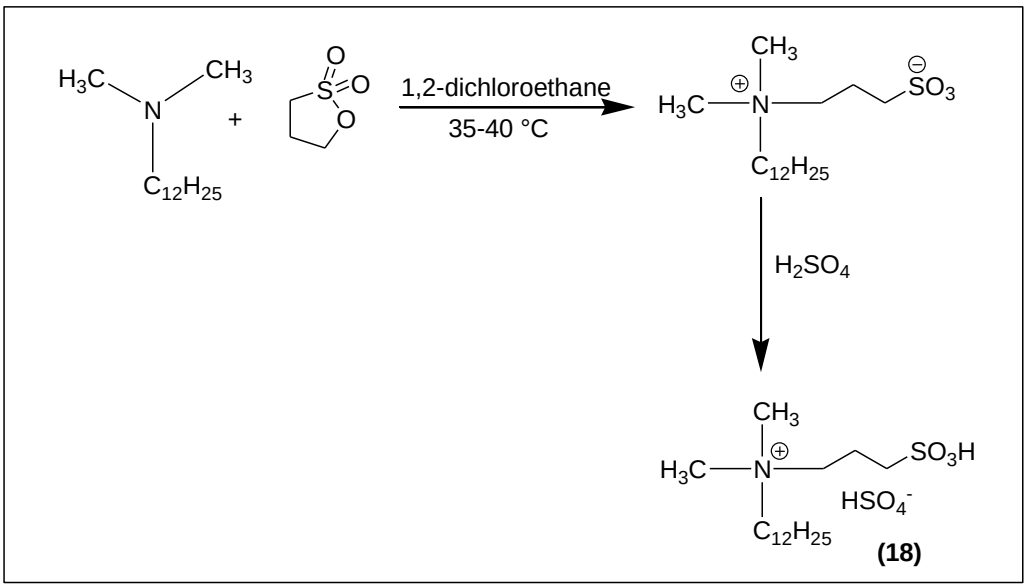


Fig.14: -SO_3H functionalized imidazolium/pyridinium based ILs

Dong *et al* in 2009 and 2013 prepared ionic liquid 3-(N, N-dimethyldodecylammonium) propanesulfonic acid hydrogen sulfate ([DDPA][HSO_4]) as reusable Brønsted acid–surfactant-combined catalyst for one-pot three-component Mannich-type reaction at room temperature in water. He prepared this sulfonic acid functionalized ionic liquid (**18)** according to **Scheme-5 [**168, 169].



Scheme-5: Synthesis of [DDPA][HSO_4]

A series of heteropolyacidic anion (HPA) based ionic system containing organic cations $[MIMPS]_3PW_{12}O_{40}$, $[PyPS]_3PW_{12}O_{40}$, and $[TEAPS]_3PW_{12}O_{40}$ in solid state (**19a-c, Fig.15**) were prepared by Shen and his co-workers and investigated their catalytic behavior in various esterification reactions [170].

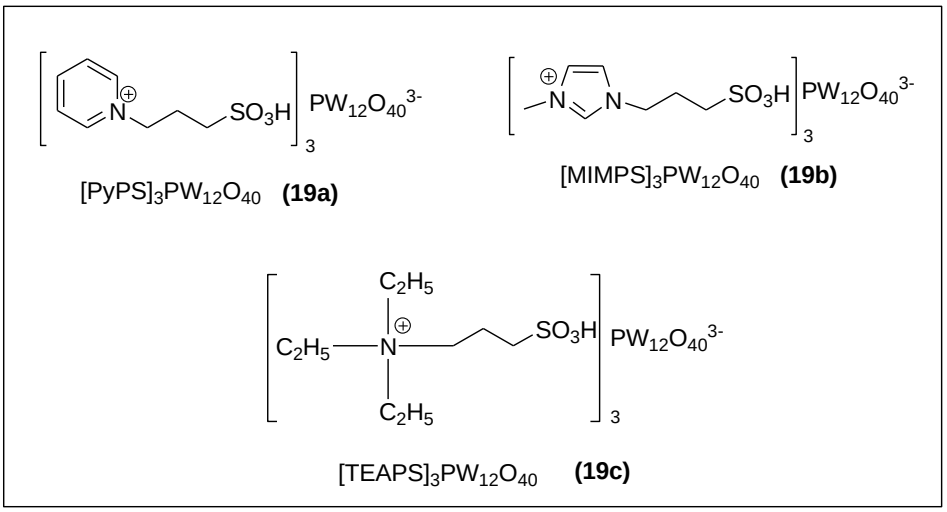


Fig.15: Ionic liquids containing heteropolyacidic anion

Amarasekara *et al* (2009 and 2014) exploited the preparation of eight different acidic ionic liquids based on 1-methyl imidazolium **(20a-b, 21)**, pyridinium **(22)** and triethanolammonium **(23)** and 1,1'-(1,4-butanediyl)-bis-imidazolium (**24)** cations, as shown in the (**Fig.16**) The catalytic activity of all the ionic liquids were investigated for hydrolysis and decomposition of cellulose in different conditions [171-172].

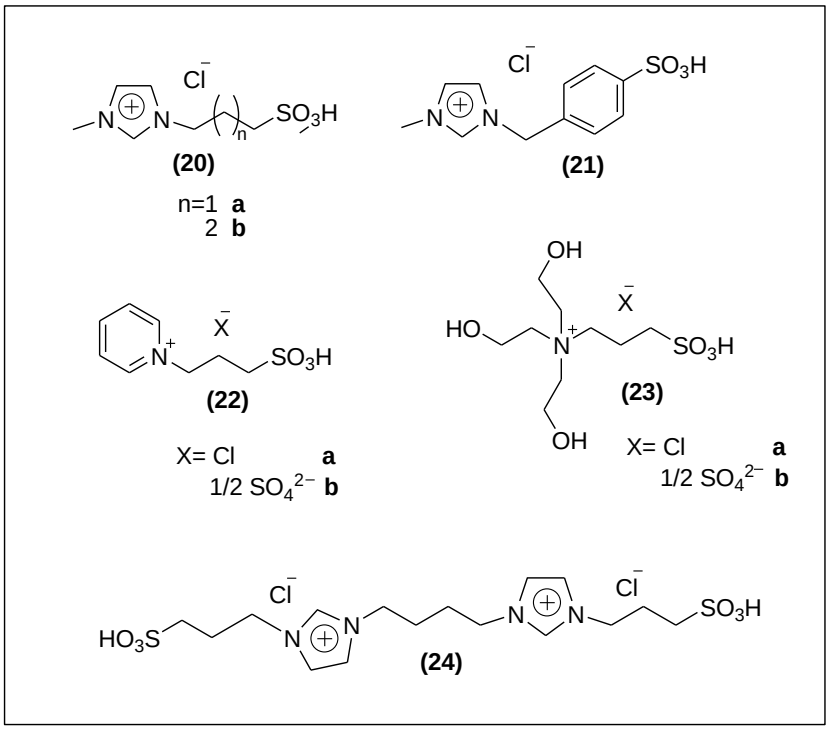
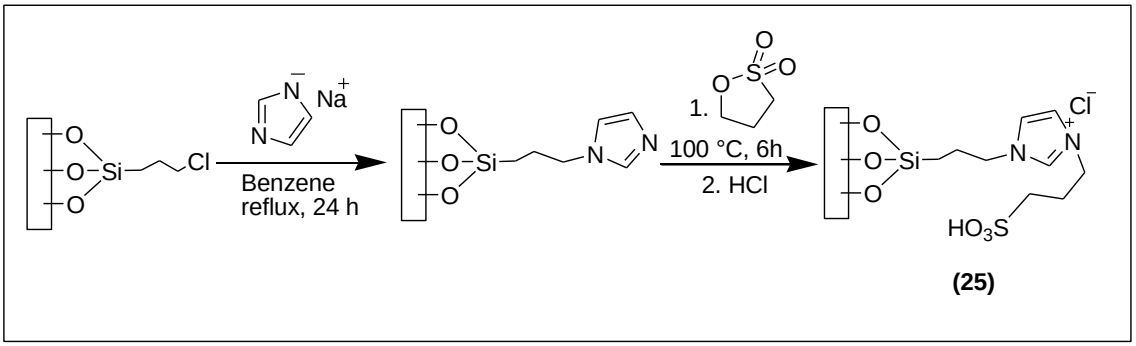


Fig.16: Structure of alkyl sulfonic group containing ILs

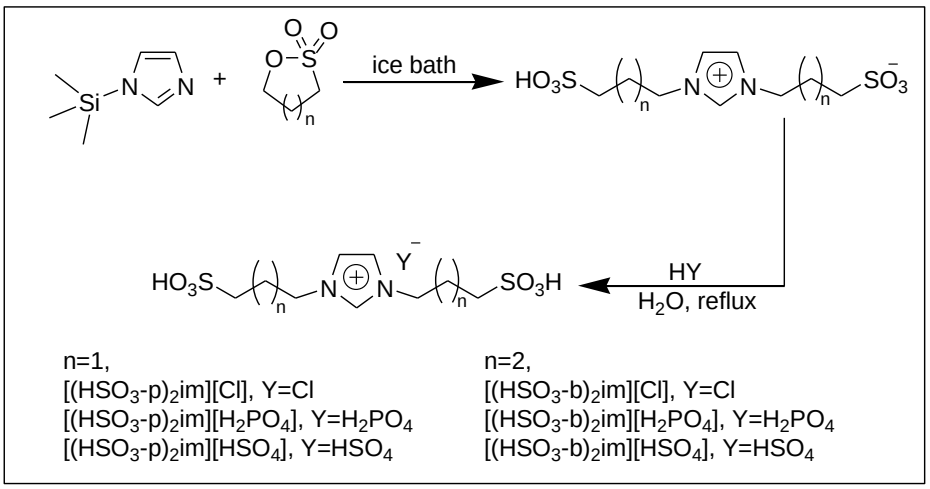
The same group also prepared (2010) sulfonic acid functionalized IL in modified silica as acidic catalyst (**25)** for the hydrolysis of cellulose. The catalyst was prepared in 68%

overall yield from 3-chloropropyl silica by a simple two step method involving nucleophilic substitution of chlorine with imidazole, followed by condensation with 1, 3-propanesultone and acidification using HCl as shown in the **Scheme-6** [173].



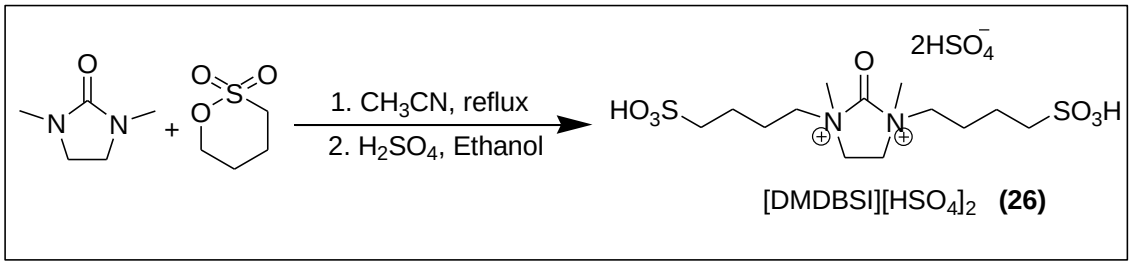
Scheme-6: Preparation of sulfonic acid functionalized IL in modified silica

Xu *et al* (2009) developed some acidic ILs bearing two alkyl sulfonic acid groups from the reaction of *N*-trimethylsilylimidazole with 1,3-propane or 1,4-butane sultone, respectively, followed by acidification of the afforded zwitterions with strong acids **(Scheme-7)**. The obtained acidic ILs was water-stable, non-volatile, and immiscible with non-polar organic solvents. The catalytic activity was investigated for the one-pot Fischer indole synthesis in water medium [174].



Scheme-7: IL synthesized from *N*-trimethylsilylimidazole

Su and his co-worker (2011) [175] prepared task specific IL 1, 3-dimethyl-2-oxo-1, 3-bis (4-sulfobutyl) imidazolidine-1, 3-diium hydrogen sulfate $[DMDBSI][HSO_4]_2$ (**26)** with two butane sulfonic groups (**Scheme-8**) and successfully applied as reusable catalyst for the three-component reactions of 10,11-dihydrochromeno[4,3-b]chromene-6,8-(7*H*,9*H*)-dione derivatives in water under reflux condition.



Scheme-8: Synthetic route of $[DMDBSI][HSO_4]_2$

In 2011 Srivastava and his group [176-177] provided the synthesis of variety of $–SO_3H$ acid functionalized imidazole/benzimidazole based acidic ionic liquids **(27a-h)** (**Fig.17)** and characterized with different analytical tool. They utilized these BAILs as reusable catalysts for esterification reaction, multicomponent synthesis of dihydropyrimidinones, amidoalkylnaphthol and Betti base compounds.

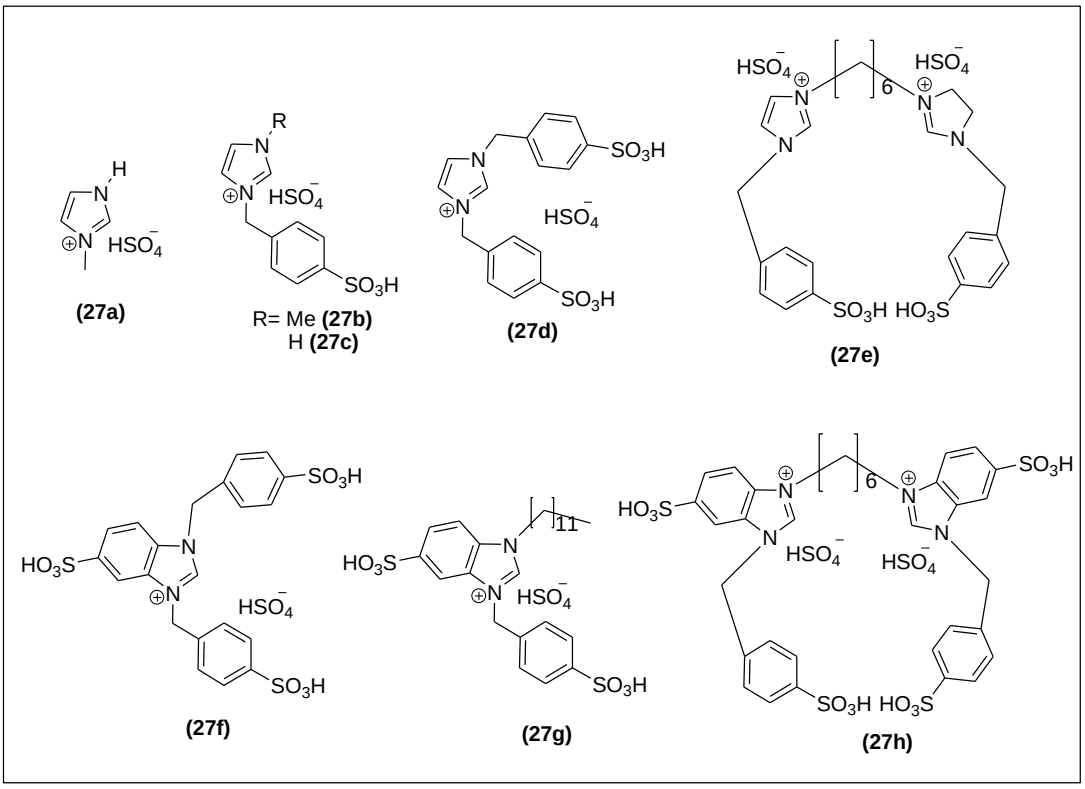


Fig. 17: Structure of imidazole/benzimidazole based ILs bearing $–SO_3H$ group

In 2011, Liu *et al* investigated the dosage of Brønsted acidic ILs (**Fig.18**) in the esterification of glycerol with acetic acid in correlation with the acidity study by the Hammett method. The influences of various reaction parameters such as reaction time, reaction temperature, and molar ratio of reactant and catalyst amount to catalytic performance were also studied [178].

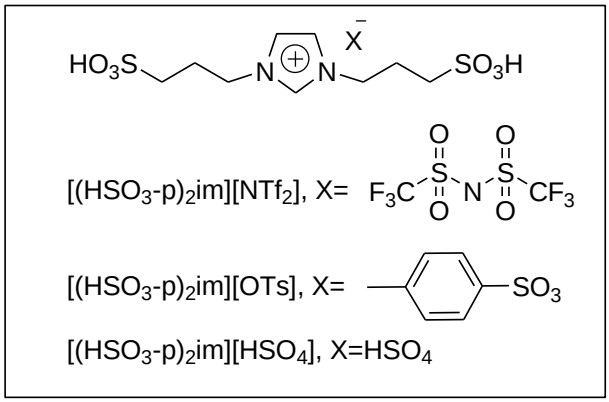


Fig.18: Structure of investigated ILs

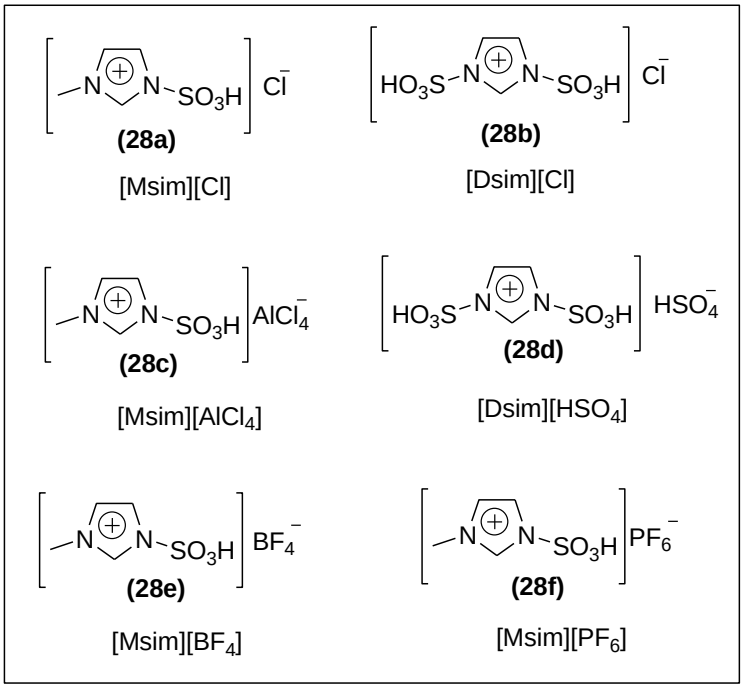


Fig. 19: Mono and di-sulfonic imidazolium based ILs by Zolfigol *et al*

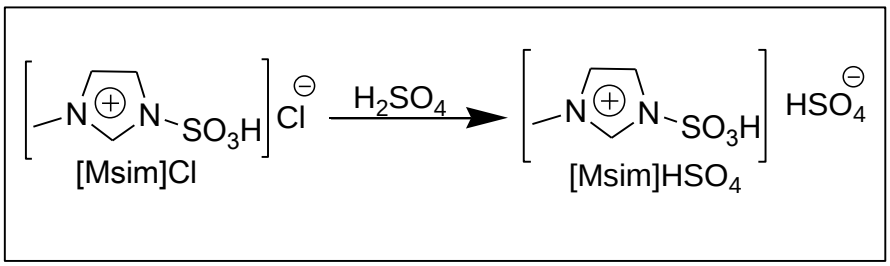
In 2010 and 2011, Zolfigol *et al* [179-182] developed three novel N-sulfonic acid containing imidazolium based ionic liquids such as 3-methyl-1-sulfonic acid imidazolium chloride [Msim][Cl] (**28a)**, 1,3-disulfonic acid imidazolium chloride [Dsim][Cl] (**28b)** and 3-methyl-1-sulfonic acid imidazolium tetrachloroaluminates [Msim][$AlCl_4$] (**28c) (Fig.19**). The basic imidazolium ionic liquids (**28a**) and (**28b**) were prepared by drop wise addition of $ClSO_3H$ to a dry CH_2Cl_2 solution of the corresponding imidazole derivatives. Addition of further equimolar amount of $AlCl_3$ to the [Msim][Cl] (**28b)** results in the formation of (**28c).** The two acidic ILs (**28b**) and (**28c**) efficiently catalyzed the one-pot three-component condensation of 2-naphthol with aromatic aldehydes and amide derivatives under solvent-free conditions to afford 1-amidoalkyl-2-naphthols in excellent

yields (81-96%) for 1-40 min reaction [171]. On the other hand the 3-methyl-1-sulfonic acid imidazolium chloride [Msim][Cl] (**28a)** acted as dual solvent-catalyst system for the efficient synthesis of bis (indolyl) methanes [180], N-sulfonyl imines [181] and nitration of phenols [182].

The same group in 2012 prepared 1, 3-disulfonic acid imidazolium hydrogen sulfate [Dsim][HSO_4] (**28d)** (**Fig.19**) by treating H_2SO_4 with 1, 3-disulfonic acid imidazolium chloride [Dsim][Cl] (**28b)** at 60 °C. This ionic liquid was applied as reusable catalyst for the N-boc protection of amines [183].

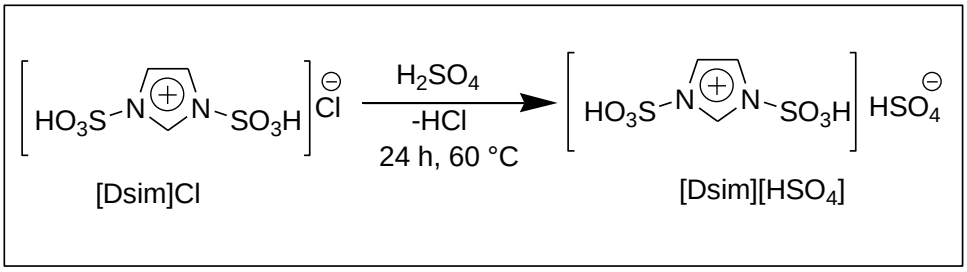
Ajjadifar *et al* [184] in 2014 synthesized [Msim][BF_4] **(28e)** and [Msim][PF_6] **(28f)** ILs bearing sulfonic groups by the metathesis reaction of [Msim][Cl] with metal salts KPF_6 and $NaBF_4$ respectively (**Fig.19**). They showed thermal stability up to 200-230 °C in TGA analysis and employed as reusable catalysts for the preparation of quinoxaline derivatives.

The preparation of (3-methyl-1-sulfonic acid imidazolium hydrogen sulfate) [Msim][HSO_4] was again reported by Khaligh *et al* (2011) [185] from the reaction of [Msim]Cl and sulfuric acid at room temperature for 8 hour (**Scheme-9**). This IL was utilized as recyclable eco-friendly catalyst for the chemoselective trimethylsilyl protection of hydroxyl groups under solvent free conditions to trimethylsilanes.



Scheme-9: Synthesis of [Msim][HSO_4] IL

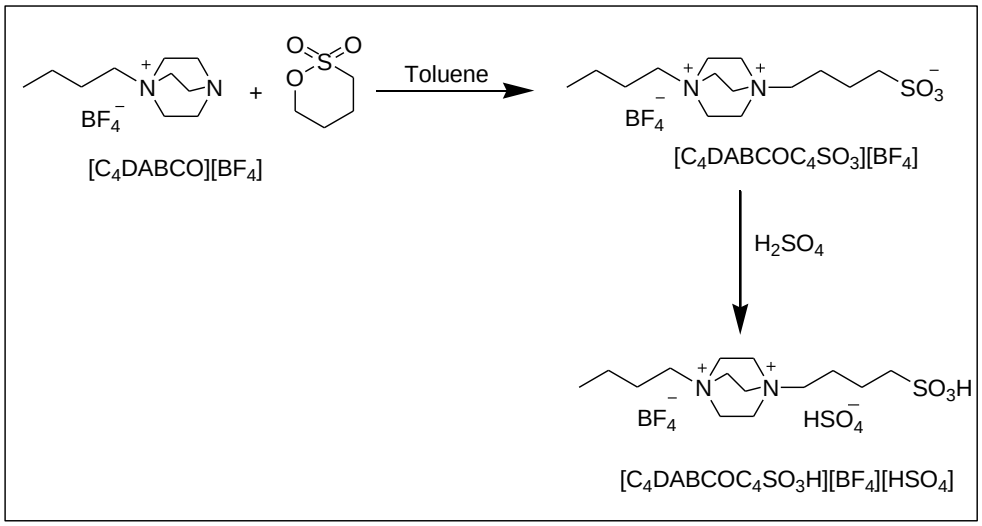
In 2012, Shirini *et al.* (2012) [186] also constructed the 1, 3-disulfonic acid imidazolium hydrogen sulfate [Dsim][HSO_4] from the reaction of [Dsim][Cl] ionic liquid and sulfuric acid (**Scheme-10**). This IL showed higher catalytic activity for the trimethylsilyl protection of hydroxyl groups at room temperature under solvent free conditions to produce trimethylsilanes.



Scheme-10. Synthesis of [Dsim][HSO_4] IL

Zare *et al* [187] also synthesized this IL in 2013 and characterized by using FT-IR, ^{1}H NMR, ^{13}C NMR, mass, TG, DTG and XRD spectra. From the TGA study the molecular decomposition of the IL [Dsim][HSO_4] was observed after 350 °C.

In the same year Davoodnia and his group [188] prepared room-temperature ionic liquid 1-butyl-4-(4-sulfonylbutyl)-1, 4-diazoniabicyclo [2.2.2] octane hydrogen sulfate tetrafluoroborate [$C_4DABCOC_4SO_3H$][BF_4][HSO_4] and studied its catalytic activity for the synthesis of dibenzoxanthene (**Scheme-11**).



Scheme-11: Synthetic route of [$C_4DABCOC_4SO_3H$][BF_4][HSO_4]

Khazaei *et al* (2012) tested [Msim]Cl/$FeCl_3$ and [Dsim]Cl/$FeCl_3$ systems in different molar ratios as catalysts to synthesized benzimidazole at room temperature in presence of air. However they failed to regenerate the catalyst system from the reaction mixture [189].

In 2012 George *et al* carried out the direct synthesis of 5-alkoxymethylfurfural ethers from fructose in presence of three mono-sulfonic acidic ILs (**20a, 29a-b, Fig.20)** as reusable catalysts. The catalysts were synthesized from the combination of 1-butylimidazole or 1-

methylimidazole with 1, 3-propanesultone and then acidification with hydrochloric acid or sulfuric acid [190].

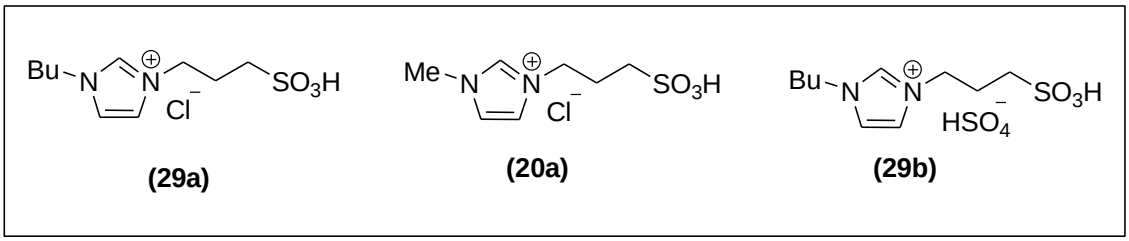


Fig.20: Propyl sulfonic acid functionalized imidazolium based ILs

In 2012, Babak *et al* prepared hydrophobic super Brønsted solid acid catalyst by incorporating a Brønsted acidic IL 1-methyl-3-octylimidazolium hydrogen sulfate [MOIm][HSO_4] of hydrophobic character into the mesochannels of SBA-15-Pr-SO_3H **(Fig.21).** After preparation they showed high catalytic activity for the solvent free esterification [191].

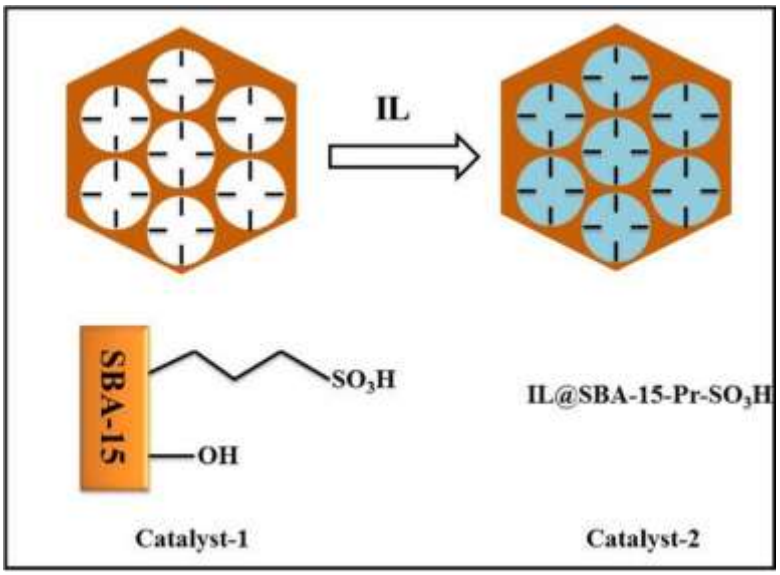
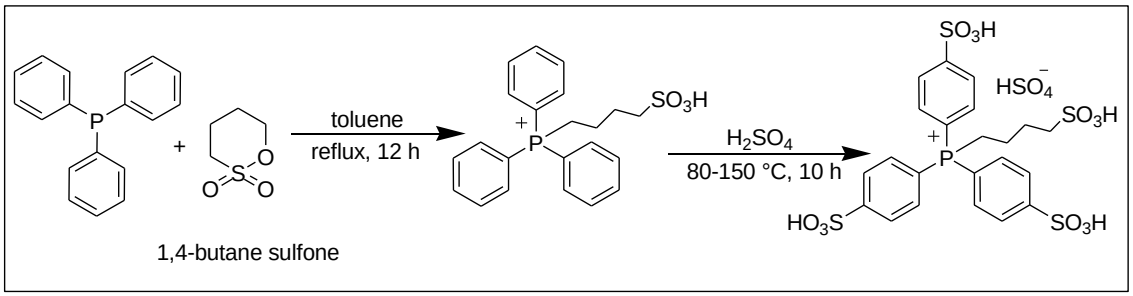


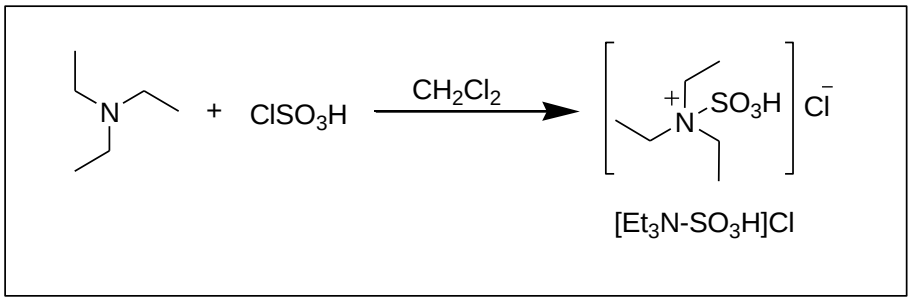
Fig.21: Schematic representation of the preparation procedure of IL SBA-15-Pr-SO_3H

Janardhan *et al* in 2012 prepared one multi –SO_3H group bearing ionic liquid (4-sulfobutyl) tris (4-sulfophenyl) phosphonium hydrogen sulphate from the zwitterions of equimolar mixture of PPh_3 and 1, 4-butane sultone in toluene under reflux and then treatment with four equivalent of H_2SO_4 at 80-150 °C for several hour (12 h) (**Scheme-12**). This task specific acidic IL was used as catalyst for the multicomponent synthesis of tetrahydrobenzoxanthene derivatives [192].



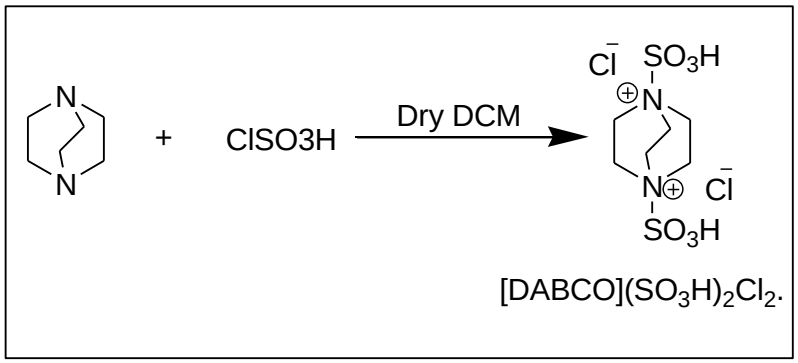
Scheme-12: Synthetic route for (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogen sulphate

Zara *et al* (2012) developed another triethylamine-bonded sulfonic acid ionic liquid [Et_3N-SO_3H][Cl] by stirring a solution of triethylamine in dry dichloromethane with drop wise addion of $ClSO_3H$ for 10 min at 10 °C [179] and it was used as a catalyst to generate library of tetrahydrobenzoxanthene derivatives via one-pot multicomponent reaction (**Scheme-13)** [193].



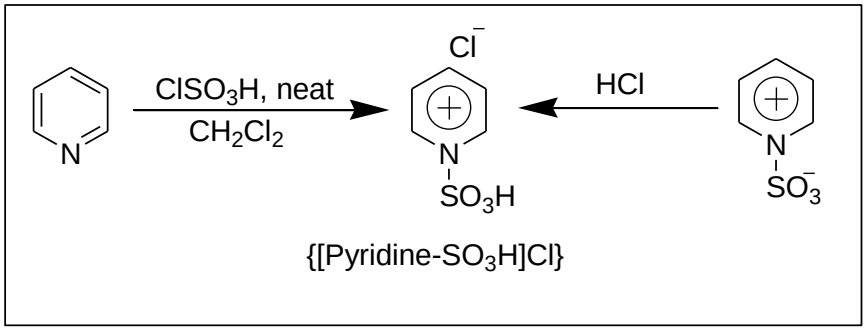
Scheme-13: Preparation of [Et_3N-SO_3H][Cl] ionic liquid

Nemati *et al* (2013) designed a novel bi -SO_3H functionalized 1, 4-diazabicyclo [2.2.2] octane (DABCO) based ionic liquid **(Scheme-14)** as acid catalyst for the synthesis of dihydropyrimidinones derivatives [194].



Scheme-14: Syntheis of DABCO based IL

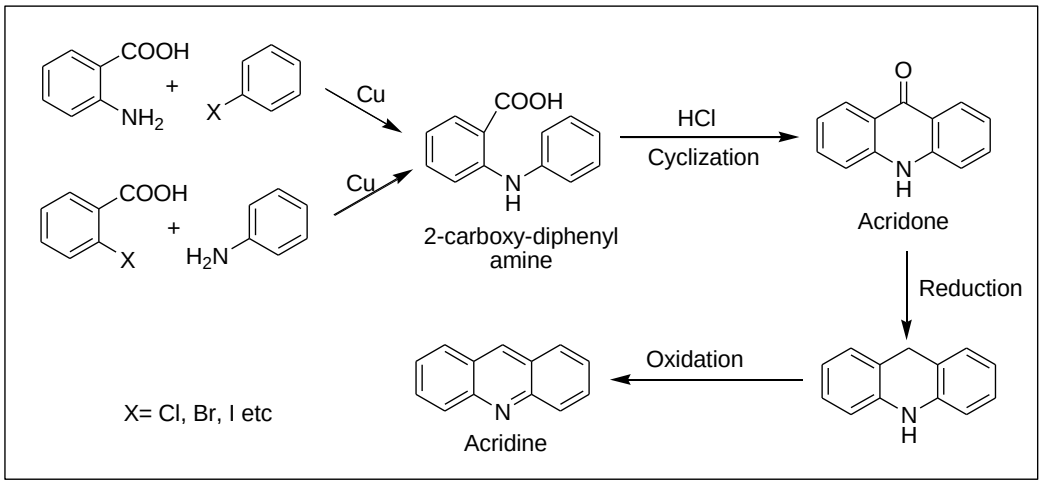
In the same year Khakyzadeh and his coworker developed a novel pyridine based -SO_3H containing ionic liquid [Pyridine–SO_3H][Cl] (**Scheme-15**) for the multicomponent synthesis of polyhydrobenzo[*a*]xanthene [195].



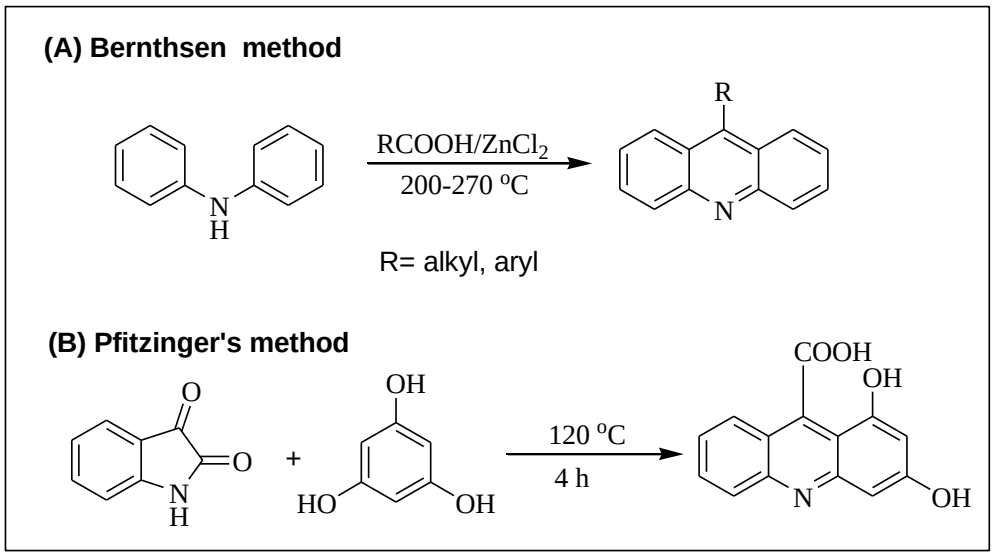
Scheme-15: Synthesis of –SO_3H functionalized pyridinium salt

1.4. Review of one-pot synthesis of 1,8-dioxodecahydroacridine, polyhydrobenzoacridine and dibenzoacridine derivatives

Acridine was first isolated as alkaloid from high boiling fraction of coal tar [196]. It has a pKa value of 5.6 which is similar to pyridine. Acridine derivatives are weakly basic in nature and express the characteristic properties of alkaloid. The common synthetic strategies of acridine nucleus include Ullmann synthesis [196-197], Bernthsen synthesis [198], Friedlander annulations [199], Pfitzinger's and Goldberg methods [200]. The Ullmann synthesis involved from either anthranilic acid derivatives or aryl halides or from 2-chlorobenzoic acid and aryl amines in four steps (**Scheme-16**). For the Bernthsen method high temperature around 200-270 °C was required (**Scheme-17).** Most of these methods were performed in presence of strong mineral acids as catalyst or reagents under reflux in organic solvent with longer reaction time. From this point of view, many alternative routes of acridine preparation have been developed using multicomponent strategies and simplified the reactions by easy isolation of product and generation of complex library of molecules with formation of minimum side products [201].



Scheme-16: Synthetic route for Ullmann acridine synthesis



Scheme-17: Common methods of acridine synthesis

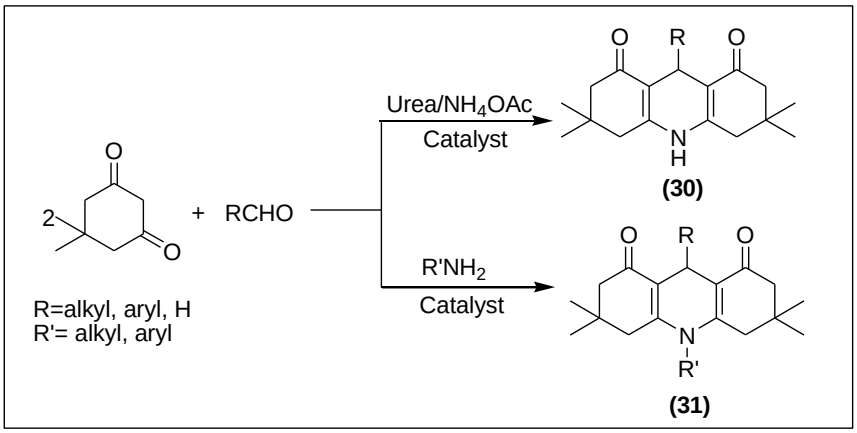
The presence of 1, 4-dihydropyrimidine (DHP) building block in 1, 8-dioxodecahydro-acridinones and polyhydrobenzoacridines provides similar properties of DHPs to these acridine derivatives [202]. The 1, 8-dioxo-decahydroacridine derivatives have been studied as polyfunctionalized 1, 4-DHPs from a variety of viewpoints such as biological activities [203-204], synthesis [205-206], physicochemical properties [207-208] and structural requirements [209]. They have been explored as calcium channel blockers and used for the treatment of defibrillation and hypertension [210]. Furthermore, they have been applied for the preparation of labelled medicinal conjugates such as nucleic acids, peptides, and proteins that exhibit antitumor and DNA-binding properties [33, 211-212].

They were also found to act as laser dyes and possess many photo physical and electrochemical properties [213].

Several substituted acridines have exhibited excellent results in the chemotherapy of cancer [214]. Therefore, the limited study of dibenzoacridines will give enormous scope to develop novel methodologies for this type of bezoacridine derivatives which may be applicable as pharmacological products or in material sciences [215]. This part of review discusses the reported procedures till 2014 in three sub units for the preparation of above mentioned three types of acridine derivatives.

1.4a. Synthesis of 1, 8-dioxodecahydroacridine derivatives

These compounds have been generally prepared by a three-component cyclocondensation of 1,3-cyclohexanone or dimedone, aldehydes and different nitrogen sources like ammonium acetate or primary amines (**Scheme-18**) via traditional heating in organic solvents in presence of various catalysts such as acetic acid [216], HCl [217], P_2O_5[218], $In(OTf)_3$ [219], $InCl_3$ [220], $ZnCl_2$ [221], triethylbenzylammonium chloride [222], Amberlyst-15 [223], $Zn(OAc)_2.2H_2O$ or *L*-proline [224], $B(C_6F_5)_3$ [225], NH_4Cl [226], *p*-dodecylbenzenesulfonic acid [227], silica-bonded S-sulfonic acid [228], MCM-4-SO_3H [229] and sulfonic acid functionalized silica [230]. Some of these decahydroacridinediones derivatives were also synthesized by the classical Hantzsch's procedures [231].



Scheme-18: Classical/general route for acridine synthesis

The literature search revealed many uses of the original acetic acid method for the preparation of different 1,8-dioxo-acridines derivatives [216, 232] with longer reaction time (2-12 h) which was introduced by Stankevich *et al* (1960) by refluxing the reaction

mixture of methylenebisdimedone derivatives (**Fig.22**) and ammonium acetate in acetic acid and produced 42-74 % of product [233].

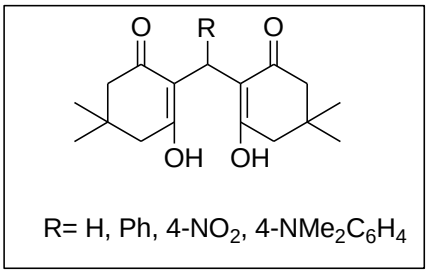


Fig.22: Methylenebisdimedone derivatives

They also mentioned the formation of 49-75 % of these compounds using the corresponding three component reactions of dimedone, aldehydes and ammonium acetate in acetic acid (**Scheme-18)**.

In another report, Greenhill *et al* (1971) observed the formation of acridinedione derivatives **(34a-b)** with 67-74% yields from methylenebisenaminones **(33a-b)** in dilute hydrochloric acid under reflux which were again derived from the reactions of primary and secondary enaminones **(32)** of dimedone with formaldehydes [217]. They also prepared other derivatives **(34c-d)** by treatment of the enaminones **(32a)** with acetaldehyde and benzaldehyde using dil. HCl **(Fig.23)**. The reaction of 3-aminocyclohex-2-enone (**32a**) with paraformaldeyde via methylenebisenaminones (**34a**) was repeated by the same author (1979) with several other Brønsted acids such as H_2SO_4, TsOH, $HClO_4$, HOAc which were as suitable as HCl acid to give the acridinedione **(35)** [234].

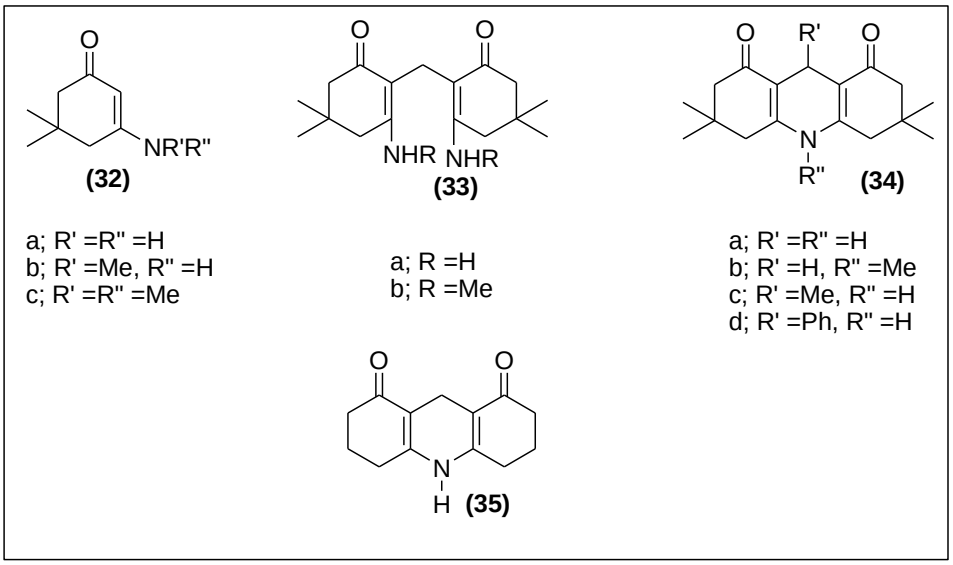


Fig.23: Synthesis of some acridine derivatives by Greenhill *et al*

Benny *et al* also (1994) followed the same route **(Fig.24**) for the condensation of 3-amino-5,5-dimethylcyclohex-2-enone **(32a)** with aryl aldehyde under reflux in ethanol within 45 min [235].

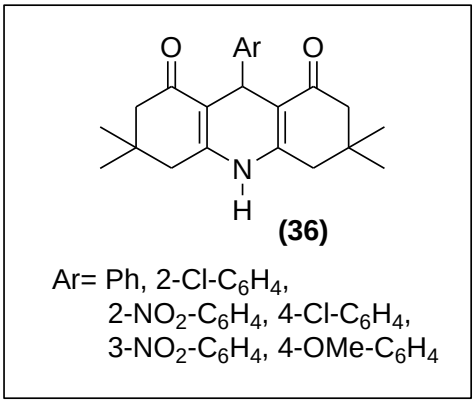
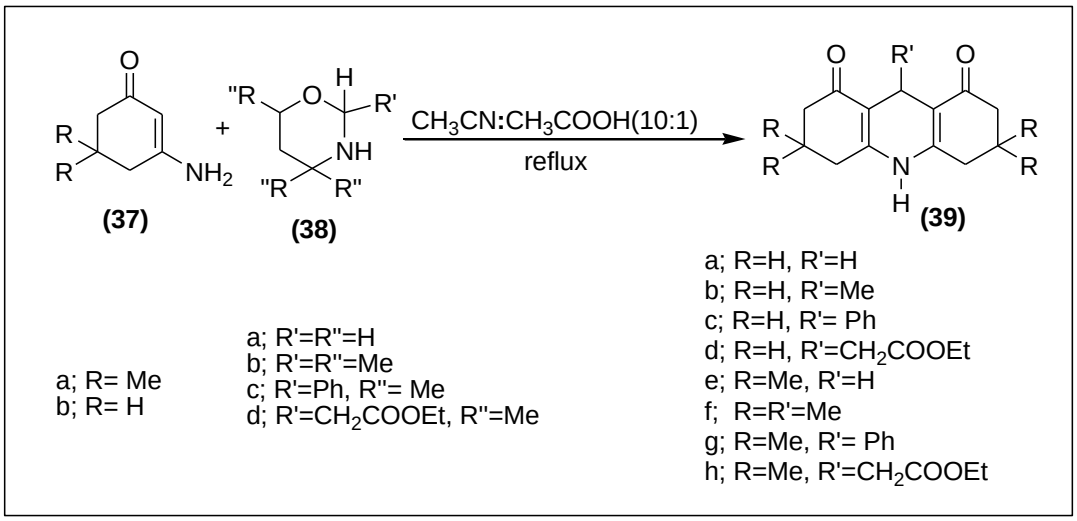


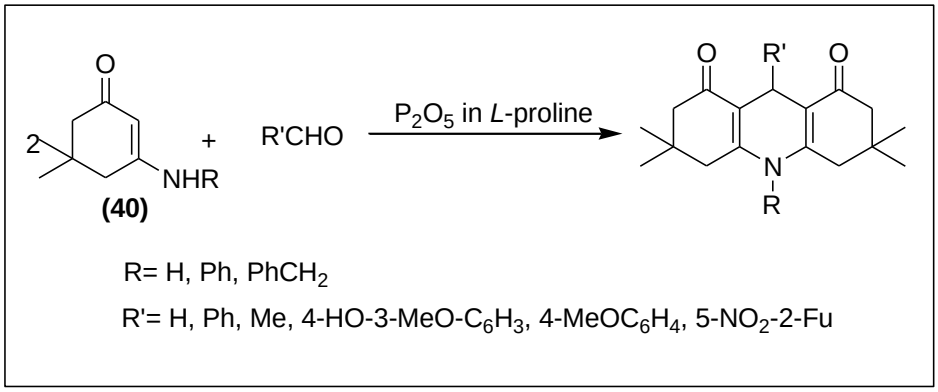
Fig.24: Acridine derivatives synthesized by Benny *et al*

In 1998, Singh *et al* prepared 62-84 % of various acridine-1, 8-dione derivatives **(39a-h)** by refluxing a solution of 3-amino-5,5–dimethyl-2-cyclohexene-1-one **(37a)** or 3-amino-2-cyclohexene-1-one **(37b)** and oxazinanes **(38a-d)** in acetonitrile : acetic acid (10:1) for 22 hour (**Scheme-19**) [236].



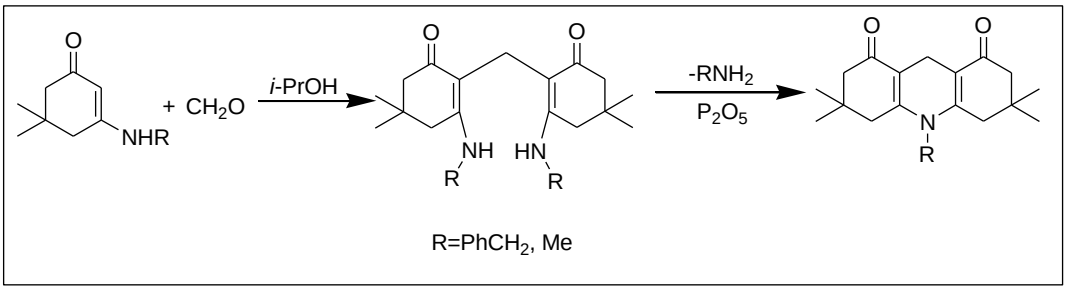
Scheme-19: Acridine derivatives reported by Singh *et al*

The application of 20% solution of P_2O_5 in isopropyl alcohol was showed by Kriven'ko and his group (2000) for the condensation of cyclic enaminoketones **(40)** containing primary and secondary N-phenyl and N-benzylamino groups, with formaldehyde, aromatic aldehydes and 5-nitrofurfural to form the acridine derivative under reflux during 2- 10 hour (**Scheme-20**) [218, 237].



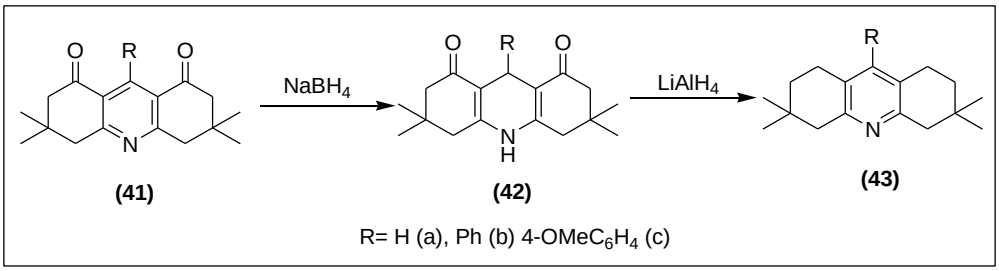
Scheme-20: P_2O_5 catalyzed synthesis of acridine derivatives

They also prepared the decahydroacridinedione in two step reactions with 91-95 % yields after thermal treatment of the bisenamino ketones in 20 % solution of P_2O_5 in isopropyl alcohol (**Scheme-21**).



Scheme-21: Synthesis of acridine from formaldehyde

In 2003, Pyrko *et al* prepared three decahydroacridinediones **(42a-c)** from the reaction of octahydroacridinedione **(41a-c)** with $NaBH_4$ for subsequent conversion to octahydroacridines **(43a-c)** in boiling diglyme (**Scheme-22**) [238].



Scheme-22: Synthesis of acridine from acridinone

Nadaraj *et al* (2007) prepared few acridine derivatives (**Fig.25**) from dimedone, 1,3-cyclohexanedione, cyclohexanone and phenol by reacting each with vinyl acetate in 2% NaOH solution followed by treatment with ammonia at room temperature for 3 hour to get 65-86% yields [239].

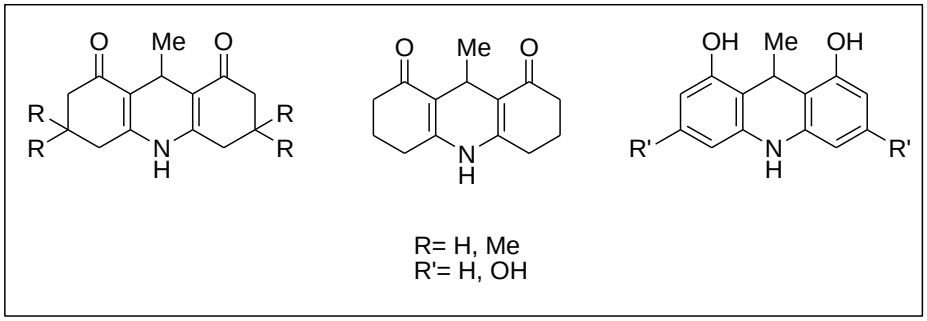
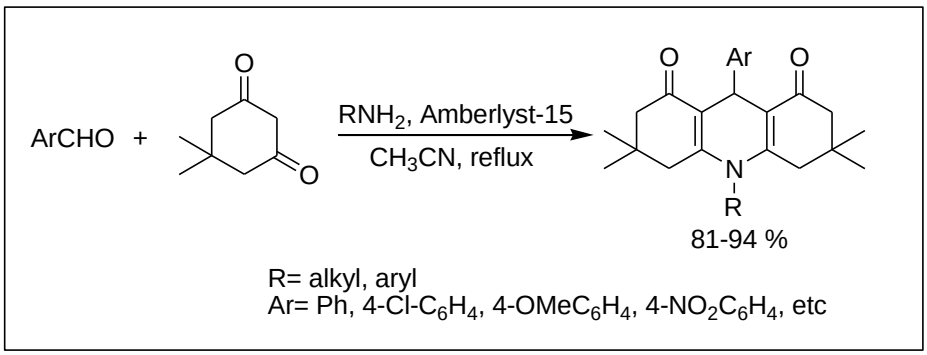


Fig.25: Acridine derivatives reported by Nadaraj *et al*

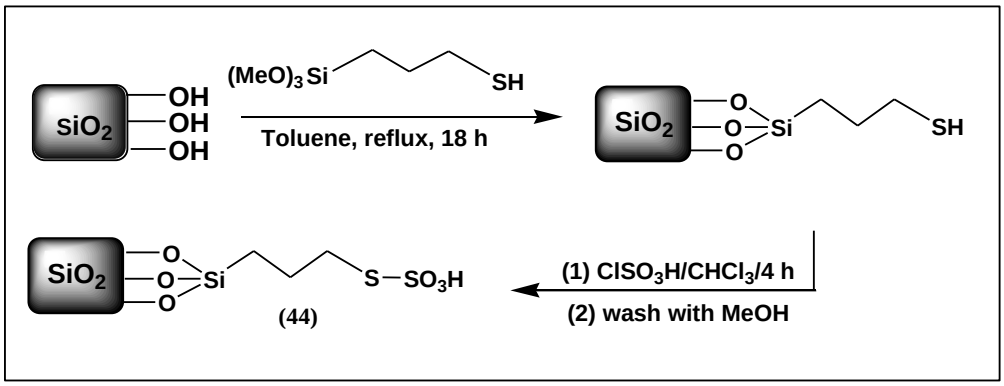
Each of these above mentioned methods often suffer from one or more disadvantages such as low yields, prolonged reaction time, use of non-recyclable catalyst and toxic solvents, harsh reaction conditions and tedious work-up procedures. Therefore several efficient, simple, safe and high-yielding methods have been introduced to improve and modify the classical three component reactions of 1,8-dioxo-decahdroacridines (**Scheme-18**). These include assistance of solvent-free reaction using thermal [240] or microwave energy [241], heterogeneous catalyst [223], in presence of greener media like water [242], polyethylene glycol [243] and ionic liquids [244].

In 2006, Das *et al* utilized Amberlyst-15 as efficient reusable heterogeneous catalyst for the preparation of 9,10-diaryl-1,8-dioxodecahydroacridines derivatives under reflux in acetonitrile during 4.5 h to 6.5 h reaction with excellent yields (**Scheme-23**) [223].



Scheme-23: Amberlyst-15 catalysed synthesis of acridinone

Niknam and his co-workers (2010) demonstrated the applications of silica-bonded S-sulfonic acid, **(44)** (SBSSA) **(Scheme-24)** as reusable solid acid catalyst for the preparation of 9,10-diaryl-1,8-dioxo-decahydroacridines under reflux in ethanol for 1-4.5 h to get 84-96 % of yields [228].



Scheme-24: Synthesis of silica-bonded S sulfonic acid

Few modified procedures for the classical reaction (**Scheme-18**) have been reported by several groups using different types of catalyst in absence of organic solvent at various temperatures. Chandrasekhar et al (2008) employed tris(pentafluorophenyl)borane [B(C6F5)3] to produce 1,8-dioxodecahydroacridines under solvent-free thermal method from the three-component reaction of 1,3-dione, aldehyde and primary amine [225].

Malaekehpoor and his co-worker (2010) performed the reactions of aniline or ammonium acetate, aldehydes and cyclic 1,3-dicarbonyl compound in 25 min at 60 °C in absence of solvent using *N,N'*-dibromo-*N,N'*-1,2-ethanediyl-*bis*-(*p*-toluenesulfonamide) (BNBTS) (**Fig.26**) as reusable catalyst with excellent yields of 1,8-dioxo-decahydroacridines [245].

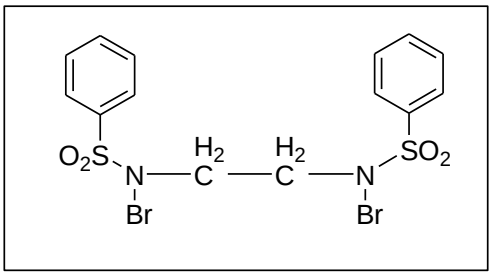


Fig.26: Structure of BNBTS

A carbon-based solid acid catalyst was used by Davoodnia *et al* (2011) for the multicomponent synthesis of 9-aryl and 9,10-diaryl substituted 1,8-dioxo-decahydroacridines at 100°C for 15-40 min reaction according to the **Scheme-18** using ammonium acetate or aromatic amines as nitrogen source to generate 80-93 % of products [246].

Davoodnia *et al* in 2012 again developed tetrabutylammoniumhexatungstate, $[TBA]_2[W_6O_{19}]$ as an efficient, inexpensive, and recyclable green catalyst for the synthesis

of decahydroacridinediones by the reaction of dimedone with aromatic or aliphatic aldehydes in the presence of ammonium acetate or aromatic amines under neat conditions at 120 °C within 7-14 min time [247]. They also utilized alumina supported polyphophoric acid (PPA/Al_2O_3) as heterogenized catalyst with excellent yields within 5- 10 min in neat at 120 °C [248].

In 2012, Yu *et al* (2012) introduced diphenylammoniumtriflate (DPAT) (**Fig.27)** as efficient catalyst for the one-pot reaction of dimedone, benzaldehyde and ammonium bicarbonate mixture under solvent-free medium at 120 °C in 3 h to form 81-96 % of 9-phenyl-1,8-dioxo-decahydroacridines [240].

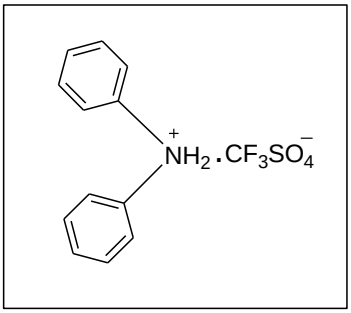


Fig.27: Diphenylammoniumtriflate (DPAT)

The use of MCM-41-SO_3H as nanocatalyst was conducted for the 9-aryl substituted 1,8-dioxo-decahydroacridines preparation in solvent-free condition by Rostamizadeh *et al* in 2012 [229].

Nakhi *et al* (2013) studied the catalytic activity of Amberlite IR-120H as reusable catalyst for the three-component reaction of dimedone, (hetero)aryl aldehydes and (hetero)aromatic amines in ethanol at 60 °C during 2-4 hour to give 73-94 % of product [249].

For the synthesis of 1,8-decahydroacridiones derivatives, Mokhtary *et al* in 2014 used polyvinylpolypyrrolidone-BF_3 (**Fig.28**) as polymer supported heterogeneous catalyst in CH_3CN in refluxing condition during 2-5-4 hour to get excellent yields of product [250]. This procedure cleanly converted a variety of aryl aldehydes with different substituent groups at *o, m,* or *p* position to the corresponding product. They utilized ammonium acetate or aromatic amines as the third component for the reaction with dimedone and aromatic aldehydes.

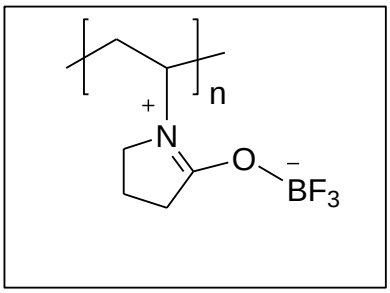
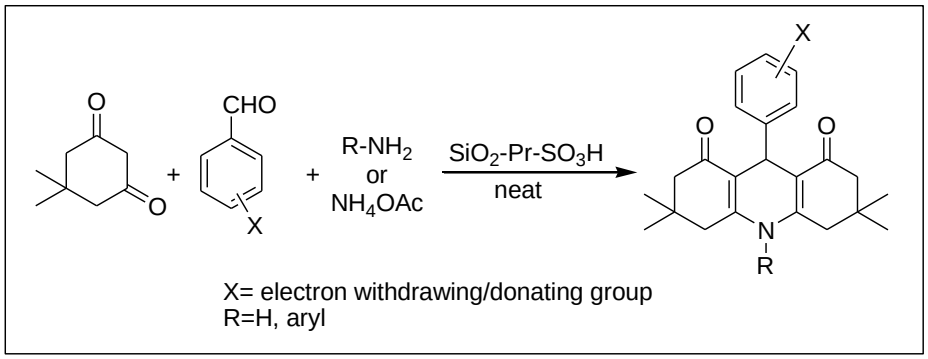


Fig.28: Polyvinylpolypyrrolidone-BF_3

A novel heterogeneous catalyst SiO_2-I was developed by Pasha *et al* (2014) and applied as efficiently for the formation of 9-aryl-decahydro-acridine-1,8-diones in ethanol at 80°C for 1.5-2.8 h reaction with 74-90 % yields [251].

Khodja *et al* (2014) utilized 20 mol% of salicyclic acid with the reaction of aromatic aldehyde and dimedone in neat condition using ammonium acetate at 80 °C during 3-5 h and obtained moderate to good yields of **(30)** [252].

Ziarani *et al* (2014) employed sulfonic acid functionalized silica (SiO_2-Pr-SO_3H) as reusable solid acid catalyst for the preparation of decahydroacridinedione derivatives in solvent-less method at 120 °C during 2 h reaction (**Scheme-25**) [230].

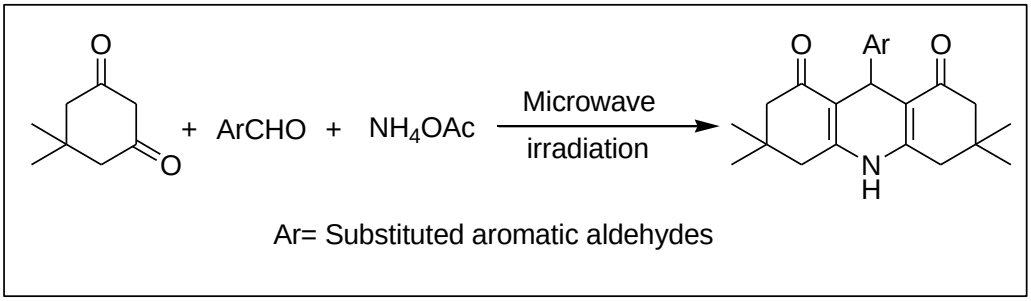


Scheme-25: SiO_2-Pr-SO_3H catalyzed synthesis of acridinone

Banerjee *et al* (2014) exploited ammonium chloride as low cost and non-toxic eco-catalyst under solvent-free medium using thermal energy for the preparation of 9,10-diaryl-1,8-dioxo-decahydroacridines via one-pot approach [226].

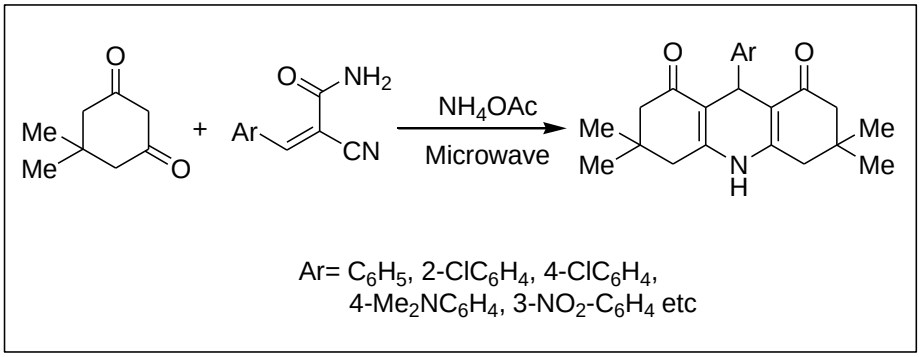
In 2014, Soliman and his co-workers applied SiO_2-$ZnCl_2$ as heterogeneous catalyst for the synthesis of both 9-aryl- and 9,10-diaryl 1,8-dioxo-decahydroacridines in neat condition at 100 °C within 30 min [253].

The first application of microwave energy for this MCRs was introduced by Suarez *et al* (1999) under solvent-free conditions using ammonium acetate supported on neutral or basic alumina and catalytic amount of *N*, *N*-dimethylformamide during short time (**Scheme-26**) [254].



Scheme-26: Synthesis of acridinone via microwave irradiation

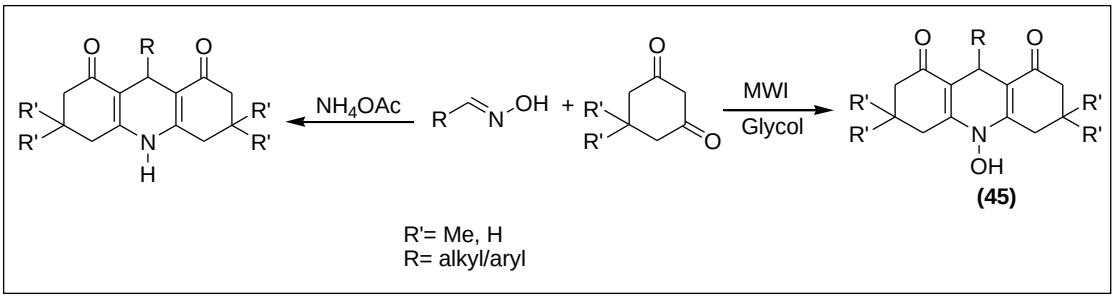
After that in 2002, Jiang *et al* used microwave irradiation in absence of solvent for the preparation of 83-92 % yield of acridinediones from the reaction of arylidenecyanoacetamide with dimedone in presence of ammonium acetate in several minutes (**Scheme-27**) [255].



Scheme-27: Synthesis of acridine derivatives via microwave irradiation

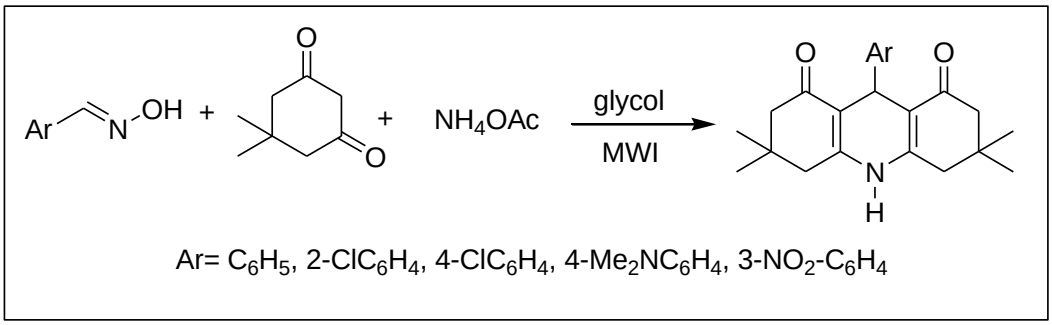
Tu *et al* and his co-workers in 2002 reported the microwave assisted three component reactions of dimedone, aromatic aldehyde and ammonium bicarbonate in neat during 4-7 min reaction to get 83-93% of the title compound [241].

The same group also published (2004) a novel sequential addition, elimination and cyclization from the mixture of aldoxime and dimedone in glycol under microwave irradiation to get a new type of *N*-hydroxylacridinedione **(45)** derivatives in excellent yields (80-95%) within a short reaction time (4-8 min) (**Scheme-28**) [256].



Scheme-28: Synthesis of N-hydroxylacridine derivatives

Tu *et al* in 2004 also modified the original reaction of aromatic aldeoxime with dimedone using ammonium acetate in glycol under microwave irradiation for the preparation of 9-aryl-1,8-dioxodecahydroacridines in 80-92 % yields within 5-6 min (**Scheme-29**) [257].

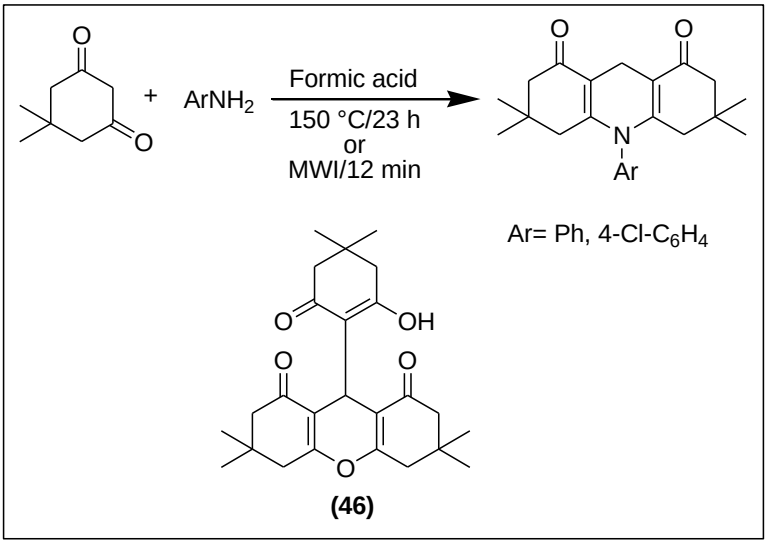


Scheme-29: Synthesis of acridinone from aldeoxime

Similarly, Perumal and his group (2003) performed a microwave initiated three component reaction of dimedone, substituted aromatic aldehyde and ammonium acetate in ethanol within 1-2 min and produced 62-94% of decahydroacridinediones [258].

Ashry *et al* (2006) carried out the synthesis of acridine derivatives after microwave irradiation of dimedone with aniline or *p*-chloroaniline in 98 % formic acid for 12 min while thermal reaction required 23 h at 150 °C for the same reaction. Under the same reaction condition, 2-aminopyridine gave the xanthene derivatives **(46)** and not the expected acridine derivatives (**Scheme-30**) [259].

Asis *et al* (2009) exploited the synthesis of 9-aryl-10-aryl-1,8-dioxodecahydroacridines from a three component Hantzsch-type condensation of different anilines with dimedone and benzaldehyde in ethanol or without solvent employing rapid microwave or conventional heating and sonication as alternative energy sources [260].



Scheme-30: Preparation of acridine derivatives in formic acid

Tang *et al* (2010) discovered a microwave assisted green procedure for the synthesis of 1, 8-dioxo-decahydroacridine derivatives without catalyst in water. This method provides several advantages such as excellent yields (86-96%), simple workup procedure, and environment friendliness [261].

Literature search reveals that the use of water as reaction medium in this one-pot reaction added several greener components such as simple purification technique, safe to handle and reduce waste materials. In 2004, Jin *et al* used *p*-dodecylbenzenesulfonic acid (DBSA) as Brønsted acid-surfactant combined environmental friendly catalyst for the three-component reactions of aromatic aldehyde, dimedone and *p*-toluidine in water to generate 9,10-diaryl-1,8-dioxo-decahydroacridines [227].

Wang *et al* (2006) performed the practical one-pot reactions of aldehydes with ammonium acetate and 1, 3-dicarbonyl compounds such as dimedone and 1,3-cyclohexanedione in water under refluxing condition without any additives to form the acridine derivatives [262].

Shi *et al* (2009) reported the use of sodium 1-dodecanesulfonic (SDS) in water as catalyst for the reaction of different aromatic aldehydes, aromatic amines and dimedone in water at 90 °C to form 56-72 % of 9,10-diaryldecahydroacridine-1,8-dione during 6 -20 h reaction [263].

In 2009, Saeed *et al* developed ammonium chloride or $Zn(OAc)_2.2H_2O$ or *L*-proline catalyzed one-pot synthesis of 1,8-dioxo-decahydroacridine derivatives in aqueous medium under reflux within 2-3 h to get high yields [224].

Nikpassand *et al* (2011) also reported the use of 15 mol% L-proline as reusable catalyst in aqueous medium for the preparation 78-92 % of 9-aryldecahydroacridine 1,8-dione at 100 °C within 2.5-3.5 h via the MCRs of **Scheme-16** [264].

In 2012, the same group again employed nano-Fe_3O_4 as reusable catalyst in water under reflux for the above cyclocondensation reactions in short time (8-15 min) to give 84-98 % of 9-aryl-1,8-dioxo-decahydroacridines [265].

Javid and his co-workers (2012) demonstrated silica-supported Preyssler nanoparticles (SPNP) as inexpensive and effective catalyst for the three-component synthesis of 9,10-diaryl-1,8-dioxodecahydroacridines in high yields (85-93%) during 2 h reaction in water under reflux condition [266].

Banothu *et al* (2013) used poly(4-vinylpyridine) hydrogen sulfate as reusable heterogeneous catalyst in aqueous medium for one-pot preparation of 1,8-acridinediones in 10-20 min at 80 °C [267].

Hong *et al* (2012) utilized catalytic amount of fluorous silica gel (FSG) supported $Hf(NPf_2)_4$ as a stable and recyclable catalyst in 50 % aqueous ethanol for the one-pot condensation reaction of aromatic aldehydes, dimedone and different aromatic amine or ammonium acetate under reflux condition within 3-7 h to obtain diverse range of acridinedione derivatives with 49-83% isolated yields [268].

Doroodmand and his group (2013) introduced a convenient and practical synthesis of 1,8-dioxo-decahydroacridine derivatives **(30)** and **(31)** using various aldehydes, 5,5-dimethyl-1,3-cyclohexanedione and thiourea in water using melamine-formaldehyde resin supported H^+(MFRH). Under solvent-free conditions, rapid and efficient synthesis of 1,8-dioxo-decahydroacridine and N-substituted 1,8-dioxo-decahydroacridine derivatives were achieved using ammonium acetate and aromatic amines as the nitrogen source [242].

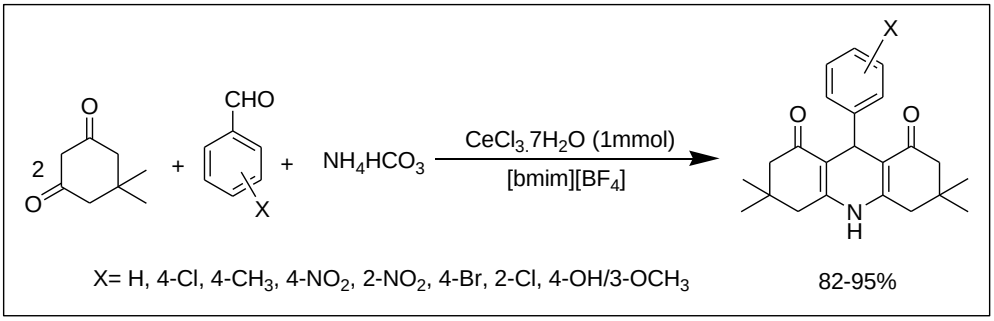
As a greener medium fluoro alcohol are solvents with peculiar properties such as low nucleophilicity, high polarity, strong H-bond donating ability and ability to solvate water. Heydari *et al* in 2009 developed trifluoroethanol (TFE) mediated one-step synthesis of Hantzsch esters and polyhydroquinolines derivatives under reflux condition. In this study, only two derivatives of 9-aryl-1,8-dioxodecahydroacridines were prepared at 70 °C during 3 h in trifluoroethanol without any additive [269].

In 2010, Kidwai and his co-worker first applied polyethylene glycol-400 as reusable medium for one-pot preparation of high yields of 9-aryl-decahydroacridine-1,8-diones from various aromatic aldehydes using 5 mol % of ceric ammonium nitrate (CAN) as catalyst during 10-25 min at room temperature stirring [243].

The trends of ionic liquid (IL) as catalyst/medium for the synthesis of 1,8-dioxo-decahydroacridines have been started from last 10 years. The first preparation of IL mediated reaction was reported by Yu-Ling *et al* in [bmim][BF_4] using aromatic aldehydes, dimedone and NH_4OAc as nitrogen source. The use of IL attributed high yields in milder reaction conditions and simplifies the work-up procedure [244].

Wang *et al* in 2006 improved the classical syntheses of 9,10-diarylacridine-1,8-dione by the reactions of 3-anilino-5,5-dimethylcyclohex-2-enones, benzaldehydes and 1,3-dicarbonyl compounds in [bmim][BF_4] ionic liquid as reaction medium. In this route the electron withdrawing and donating group containing aniline gave excellent yields under the optimized reaction condition [270].

The same group in 2007 again utilized [bmim][BF_4] ionic liquid as reusable medium in combination with 5 mol% of $CeCl_3.7H_2O$ as catalyst for the preparation of 9-arylacridine-1,8-dione derivatives in two step one-pot reactions at 55 °C and 100 °C respectively during 6 h reactions (**Scheme-31**) [271]



Scheme-31: [bmim][BF_4] ionic liquid catalyzed synthesis of acridine derivatives

Shi *et al* (2008) prepared both of 9,10-aryl substituted and 9-aryl or alkyl substituted 1, 8-dioxodecahydroacridines from the reaction of aldehyde, dimedone and aromatic amine or ammonium acetate in [bmim][Br] IL medium at 90 °C. The formation of 9,10-diaryl-substituted derivatives required more time (2.0-4.5 h) as compared to N-unsubstituted acridinedione (15-60 min) [272].

Firoz and his coworker (2011) used the same [bmim][BF_4] ionic liquid for the synthesis of isoxazolyl polyhydroacridinedione from the reaction of aldehyde, dimedone and isoxazolyl amine that results 80-95 % of yield within 1.0-2.5 h [273].

Vahdat and his co-workers (2011) employed 1 mol% of multi –SO_3H groups containing triphenylphosphinium based ionic liquid (as mentioned in **Scheme-12**/Section 1.3) as catalyst for the synthesis of **(30)** and **(31)** derivatives of 1,8-dioxo-decahydroacridines under ambient temperature in water via one-pot condensation reaction during 5-21 min duration with excellent yields [274].

In 2014, they also observed the same reaction in water using heteropolyanion bearing solid ionic systems $[MIMPS]_3PW_{12}O_{40}$ and $[TEAPS]_3PW_{12}O_{40}$ (**19b-c, Fig.15**/Section 1.3) as excellent within one hour reaction time [275].

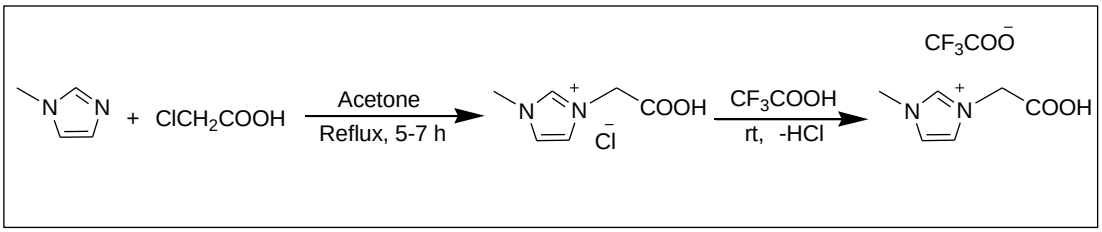
Dabiri *et al* in 2008 investigated the catalytic activity of Brønsted acidic 1-methylimidazolium trifluoroacetate ([Hmim]TFA) ionic liquid for the 9,10-diaryl-1,8-dioxo-decahydroacridines at 80 °C using 35 mmol of IL. This IL mediated reaction required 4-7 h reaction to yield 78-89 % of product and the IL was reused for four runs without loss of activity [276].

Yu and his group (2009) developed two Brønsted acidic imidazolium salts containing perfluoroalkyl tails **(16a)** and **(16b)** (as shown in the **Fig.13**/Section 1.3) as Brønsted acid-surfactant combined catalyst for the 9,10,-diaryl-1,8-dioxo-decahydroacridine derivatives with good yields (79-91%) in water under reflux condition for 4 h. The method provides several advantages such as low catalyst loading (1-1.5 mol %), recycle of the catalyst and simple work procedure [166].

A homogeneous ionic liquid [bmim][BF_4] doped with 0.5 mol% $Mg(BF_4)_2$ was used by Rad-Moghadam *et al* (2012) for the synthesis of 9-aryl-1,8-dioxo-decahydroacridines at 80 °C during 15-30 min which showed 84-90 % of product and the catalyst were reused

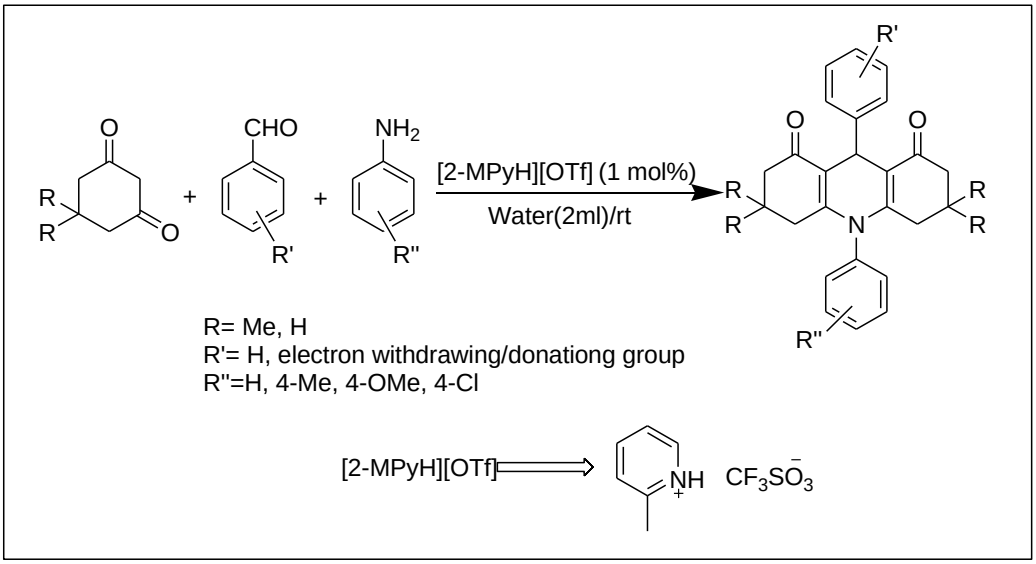
for several times after separation from the reaction mixture using water extraction method [277].

Patil et al (2014) used 30 mol% of 3-(carboxymethyl)-1-methyl-1H-imidazol-3-ium-trifluoroacetate [CMIM][CF_3COO] acidic ionic liquid as recyclable homogeneous catalyst in 50% aqueous ethanol at 80°C during 1-1.5 h time for the synthesis 81-90 % of 9-aryl-1,8-dioxodecahydroacridine derivatives (**Scheme-32**) [278].



Scheme-32: Synthesis of 3-(carboxymethyl)-1-methyl-1H-imidazol-3-ium-trifluoroacetate

Alinezhad *et al* (2013) performed the preparation of 9,10-diaryl substituted 1,8-dioxo-acridines in water within 7-20 min using reusable 1 mol % of [2-MPyH][OTf] at room temperature to form 91-98 % yields (**Scheme-33**) [279].



Scheme-33: Synthesis of 9,10-diaryl substituted 1,8-dioxo-acridines

1.4b. Synthesis of polyhydrobenzoacridine-1-one derivatives

The chemical modifications of acridinedione derivatives have extended the study of structure-activity relationship of DHPs derivatives into the molecular–receptor levels which have similarities in structure to the biologically important compounds such as

NADH and NADPH [216]. Several benzoacridines possess antitumor properties by intercalation of the plane aromatic ring with DNA molecules and they are also active against DNA topoisomerases [280-281]. Martinez *et al* [282] revealed an appreciable cytostatic activity of partially hydrogenated benzoacridine compounds.

In 1971, Lielbriedis *et al* discussed the reactions of various aromatic aldehydes with equivalent amounts of 1-naphthylamines and dimedone under thermal treatment for 20-150 min and proposed the structure of the product as **(47)**. Later on oxidation of **(47)** with CrO_3 in AcOH gave the corresponding oxidized product **(48)** (**Fig.29**) [283].

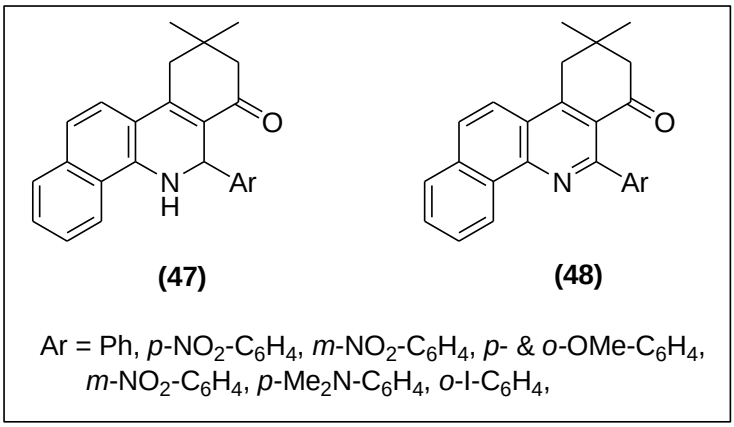


Fig.29: Structure of polyhydrobenzo[a]acridine-1-one derivative

In 1988, Cortes and his co-workers [284] attempted to synthesize 5-aryl-5,6,7,8,9,10-hexahydrobenzo[*c*]phenanthridin-7-ones **(49)** from the reaction of dimedone to a solution of α-arylidennaphthylamines in ethanol or benzene through 1,4-addition and then oxidation by chromic anhydride to its corresponding tetrahydro derivatives (**50) (Fig.30)**

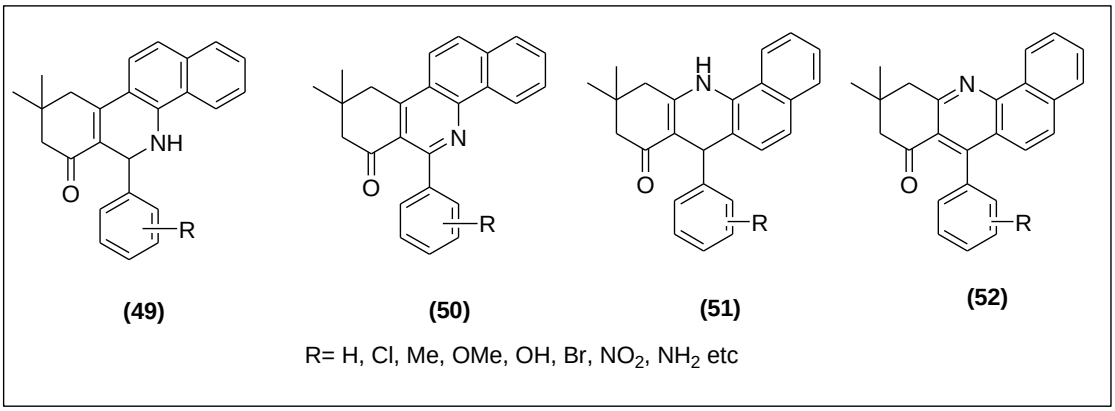


Fig.30: Polyhydrobenzo[a]acridinone from 1- and 2-naphthol

However, the attempted preparation of these compounds resulted instead of the formation of isomeric benzo[c]acridin-8-ones **(51)** and tetrahydrobenzo[c]acridin-8-one **(52)**. Structures were confirmed by FT-IR, ^{1}HNMR, MS and X-ray spectroscopy.

Martínez *et al* (1990) confirmed that the reaction of β-naphthylamine, dimedone and an appropriate aromatic aldehyde in ethanol under reflux yielded benzo[a]acridin-11-one **(54)** instead of 1,2,3,4,5,6-hexahydro-2,2-dimethyl-5-aryl-6-aza-9,10-benzophenanthren-4-ones **(53)** which upon treatment with chromic anhydride, converted to the corresponding tetrahydro derivatives (**55) (Fig.31)** [285]. But the product of this multicomponent reactions was identified as **(53)** by Lielbriedis *et al* **(1971)** as those obtained earlier for the 1-naphthylamines [283].

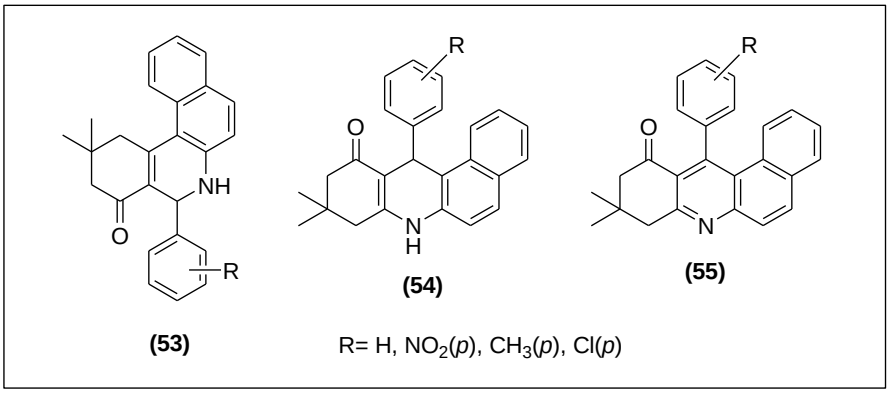
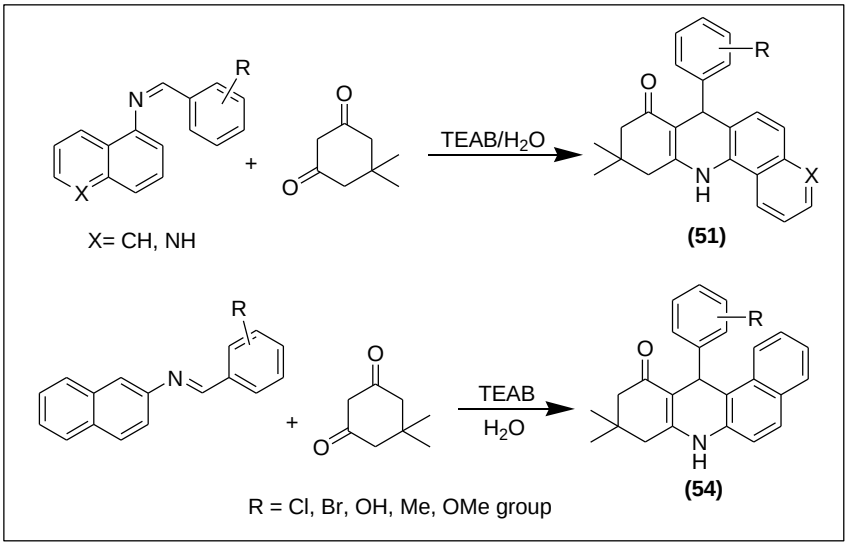


Fig. 31: Polyhydrobenzo[a]acridine derivatives synthesized from β-naphthylamine

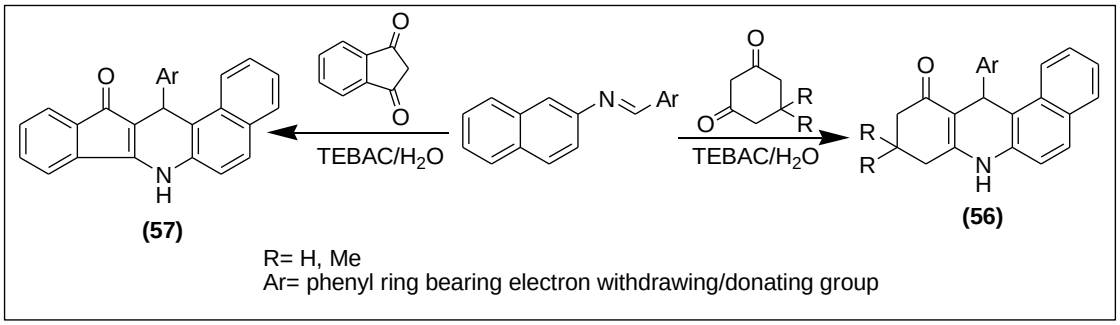


Scheme-34: TEAB catalyzed synthesis of polyhydrobenzo[a]acridinone in water

Wang and his group in 2005 and 2006, developed a clean and simple synthesis of benzo[c]acridine **(51)**, and benzo[a]acridine **(54)** derivatives via the reaction of N-

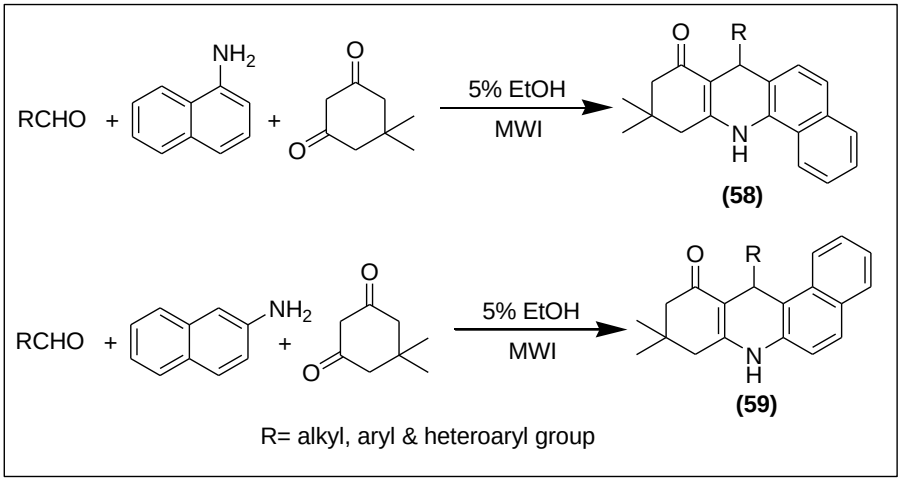
arylidenenaphthalen-1-amine or N-arylidenenaphthalen-2-amine with dimedone in aqueous medium using 37 mol% (100 mg) of benzyl triethyl ammonium chlorides (TEBA) as non-recyclable catalyst in water at 100 °C for several hour (**Scheme-34**). The reaction of benzo[c]acridines required more time (12-24 h) to produce 76-98 % of products whereas benzo[a]acridine formed 87-99% yields during 2-12 h under the optimized condition [286-287].

In 2006, Wang et al again utilized the same catalyst as triethylbenzylammmonium chloride (TEBAC) with varieties of aromatic aldehydes at 100 °C in water for the synthesis of benzo[*a*]acridines **(56)** and indeno[1,2-*b*]benzo[*f*]quinolines **(57)** in high yields (81-99%) from the reaction of *N*-arylidenenaphthalen-2-amine with 1,3-dicarbonyl compounds for 2-12 hour (**Scheme-35**). This method provides several advantages such as neutral conditions, high yields and simple work-up procedure [288].



Scheme-35: Synthesis of polyhydrobenzo[a]acridinone from triethylbenzylammmonium chloride

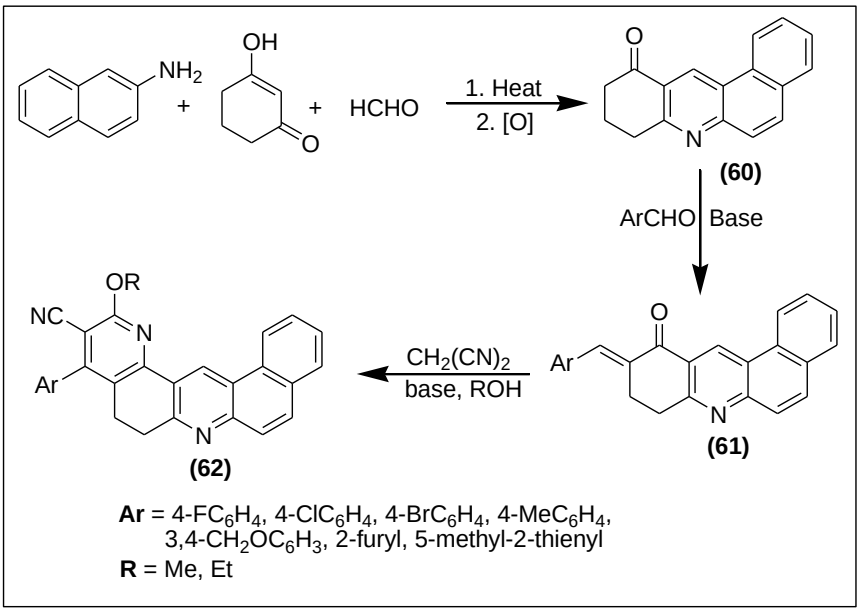
The use of microwave energy was studied by Tu *et al* (2006) to synthesize a series of 3,3-dimethyl-9-substituted-1,2,3,4,9,10-hexahydrobenzo[*c*]acridine-1-ones **(58)** and 3,3-dimethyl-9-substituted -1,2,3,4,9,10-hexahydro benzo[*a*]-acridine-1-ones **(59)** from the reaction of equimolar amount of aldehyde, 1-naphthylamine or 2-naphthylamine and dimedone in small amount of ethanol (95%) within short time and high yields (75-98%) (**Scheme-36**) [289].



Scheme-36: Synthesis of benzoacridinone in ethanol under MWI

Besides, compared with the traditional heating method in ethanol, the reaction time was shortened to 5-19 min under microwave condition from 2-12 h [286-287]. This protocol can be applied not only for the aromatic aldehydes with either electron-withdrawing groups or electron-donating groups, but also for heterocyclic and aliphatic aldehydes.

Bondarev and his co-worker (2006) synthesized a series of partially hydrogenated benzo[a] acridine derivatives according to **Scheme-37** from 8,9,10,11-tetrahydrobenzo[a]acridin-11-one **(60)** as starting material with aromatic aldehydes in multistep routes [290]. The ketone **(61)** was prepared from triple condensation of 2-naphthylamine with formaldehyde and cyclohexane-1,3-dione in ethanol under thermal condition, followed by oxidation using chromium (VI) oxide in acidic solution.



Scheme-37: Synthesis of biologically active benzoacridinone

In 2009, Mohan and his co-worker carried out the preparation of some new substituted tetrahydroacridin-8-ones and diverse derivatives under microwave energy through three component reaction of dimedone or cyclohexan-1,3-dione, 1-naphthylamine or 2-naphthylamine and various (*o*,*p*,*m*)-substituted benzaldehydes for 2-5 min to give excellent yields (91.9-98.1%) of **(58)** or (**63)** derivatives **(Fig.32)**. The results of in vitro anti-microbial activities suggested that, the products **(58a–g)** and **(63a–g)** exhibited good inhibitory effect against most of the tested organisms. Especially **(58f)**, **(58g)**, **(63f)** and **(63g)** were shown to be most effective against Rhodotorula rubra and Aspergillus parasiticus and compounds **(58a)**, **(58c)**, **(58g)**, **(63f)** and **(63g)** proved to be effective with MIC values in the range of 3.9–7.8 mg/ml [291].

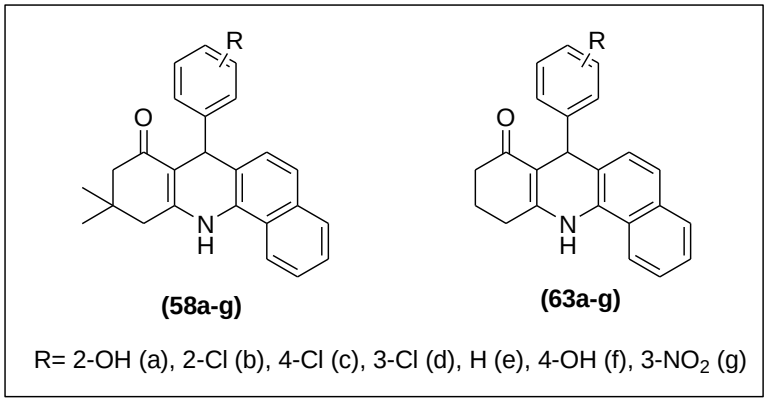
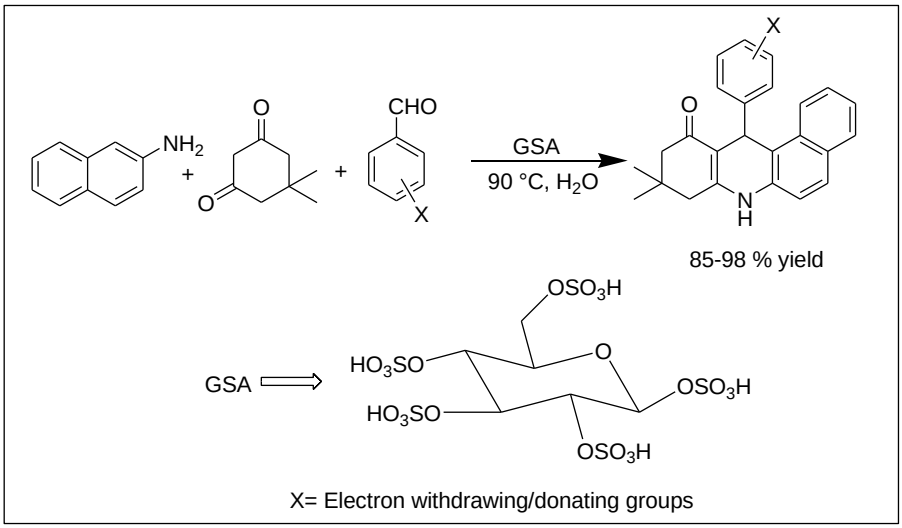


Fig.32: Polyhydrobenzo[a]acridinone under MWI

Wu and his coworker in 2013 employed 5 mol % of glucose sulfonic acid **(GSA, Scheme-38)** as non-reusable liquid acidic catalyst for the multicomponent synthesis of tetrahydrobenzo[a]acridine derivatives in water at 90 °C for 4-10 hour [292].



Scheme-38: GSA catalyzed synthesis of polyhydrobenzo[a]acridinone

From this literature review it was observed that till date no methods are available for the synthesis of tetrahydrobenzo[a] acridines derivatives in ionic liquid as catalyst or medium and using any recyclable greener catalysts. In addition the reported methods available in literature have utilized 1- or 2-naphthylamine only and either via two or three component reaction. In this context, we aimed to develop some task-specific acidic ionic liquid catalyzed/mediated methodologies for the four component synthesis of title compounds using 2-naphthol as one of the starting materials within the framework of green chemistry principles.

1.4c. Synthesis of dibenzoacridine derivatives

Dutta *et al* in 2003 prepared 9-phenyl-9,10-dihydroacridine **(68a-b),** 7-phenyl-7,12-dihydrobenzo[*c*]acridine **(69a-b),** 7-phenyl-7,14-dihydrobenzo[c,h]acridine **(70a-b)** derivatives with good to moderate yields by phenylation of acridine **(64)**, benzo[c]acridines **(65)** and dibenzo[*c*,*h*]acridine **(66)** respectively in dry THF at 0 °C with phenyllithium-TMEDA followed by quenching the reaction mixture with water or D_2O (**Fig.33**) [293]. Changing the quenching agent to CH_3I or C_2H_5Br led to the incorporation of a methyl or ethyl group onto the nitrogen for all derivatives such as **(68c-d)**, **(69c-d)**, and **(70c-h)**. However with isopropyl bromide, *N*-alkylation was not observed. An interesting observation was noticed in case of dibenzo[*c*,*f*]acridine **(67)**, where no phenylation was observed.

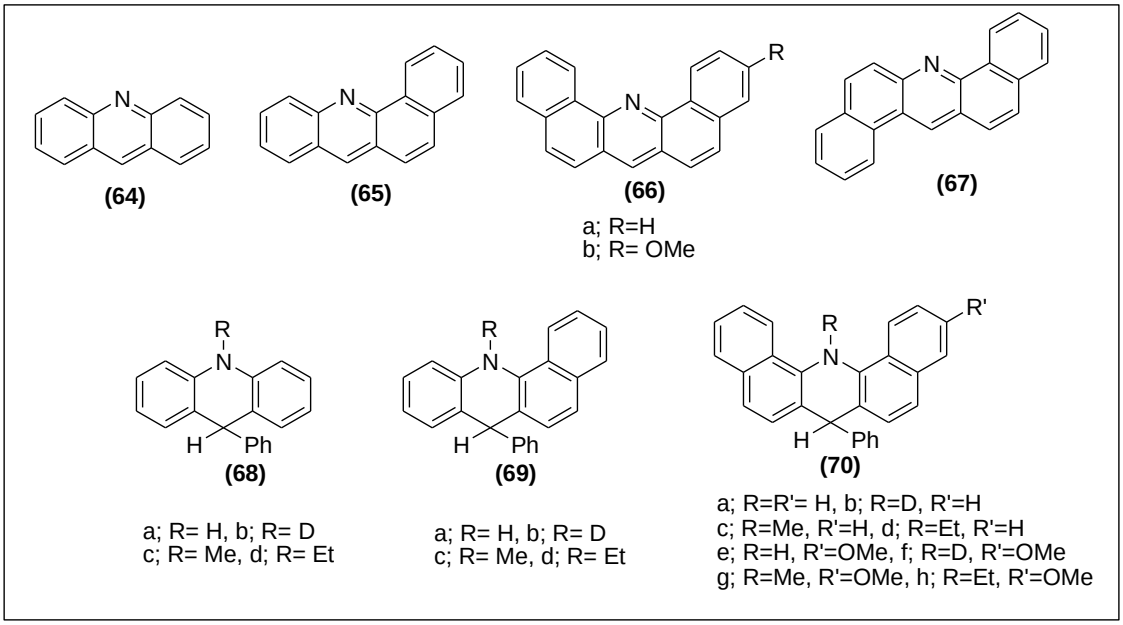
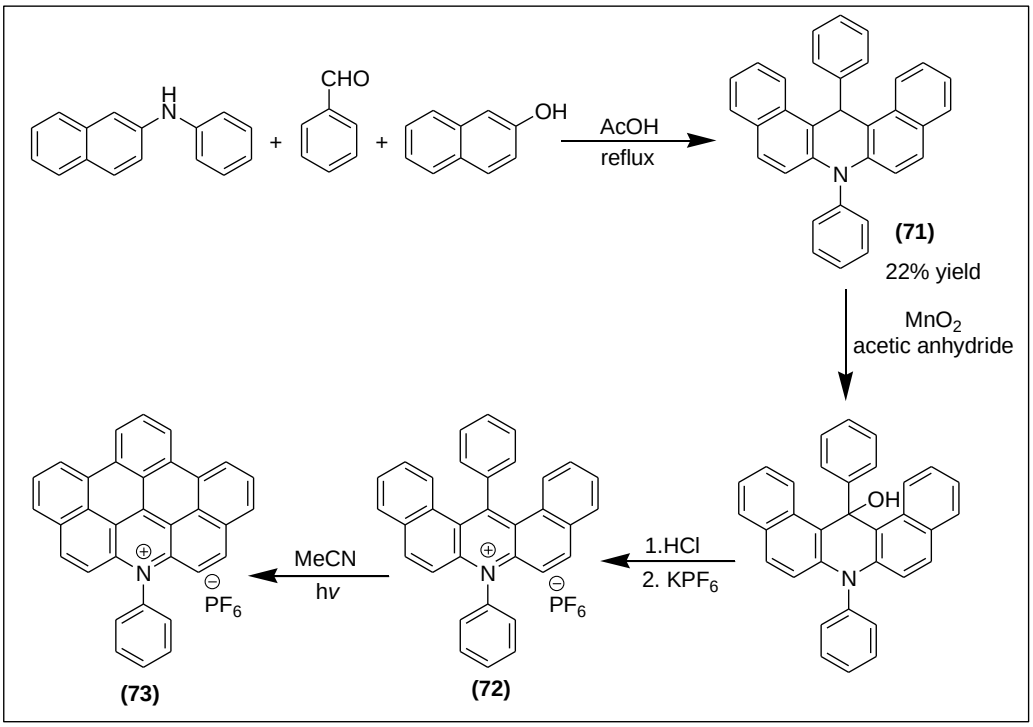


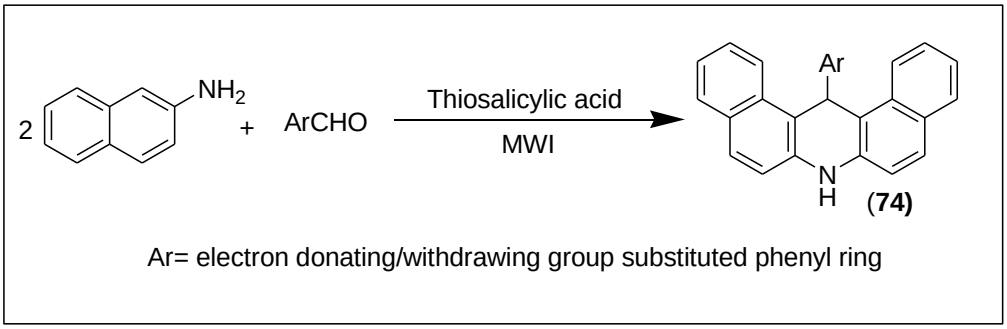
Fig.33: Some of the reported dibenzoacridine derivatives

In 2006, Benniston *et al* identified one derivative of dibenzoacridine **(71)** as reaction intermediate with 22 % yield from the multicomponent reaction of 2-naphthol, N-phenyl-2-naphthylamine and benzaldehyde in glacial acetic acid under reflux condition towards the synthetic strategies of highly strained no-luminescent dibenzo-acridinium cationic compounds **(72)** (**Scheme-39**). This compound again produced a highly fluorescent, planar, eight-ringed cationic anti-aromatic dye **(73)** in acetonitrile via light-induced ring closure reaction [52].



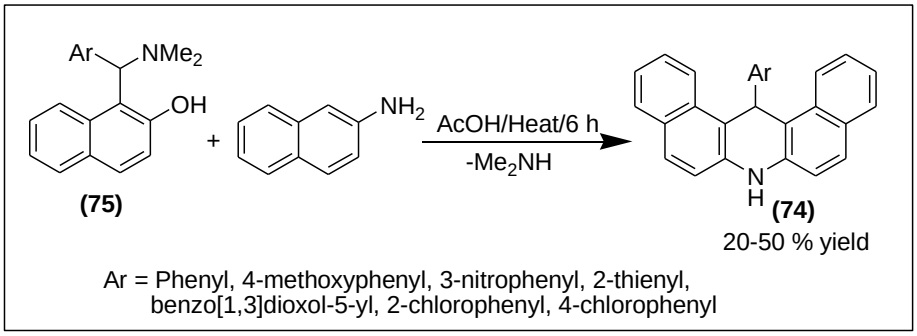
Scheme-39: Formation of dibenzoacridine intermediate **(71)**

Tu and his co-worker in 2010 reported thiosalicylic acid catalyzed synthesis of angular fused aza-heterocycles dibenzoacridine (**74)** via microwave irradiation using multicomponent approach **(Scheme-40)**. The procedure produced 72-89% yield of the compound that exhibited good luminescent properties [51].



Scheme-40: Thiosalicylic acid catalyzed synthesis of dibenzoacridine

Recently, Osyanin *et al* (2014) developed a methodology to synthesize 14-aryl-7,14-dihydrodibenzo[*a*,*j*]acridine under reflux condition in glacial acetic acid by treating 2-naphthylamine with Mannich base **(75)** (Betti base) for 6 hour in argon atmosphere to produce 20-50 % yields of **(74)** (**Scheme-41**) [294]. The Betti bases were synthesized from the mixture of 2-naphthol, aromatic aldehyde and dimethylamine in ethanol for 4 days stirring at room temperature, followed by 3 hour at -20°C according to the known procedure [295-297].

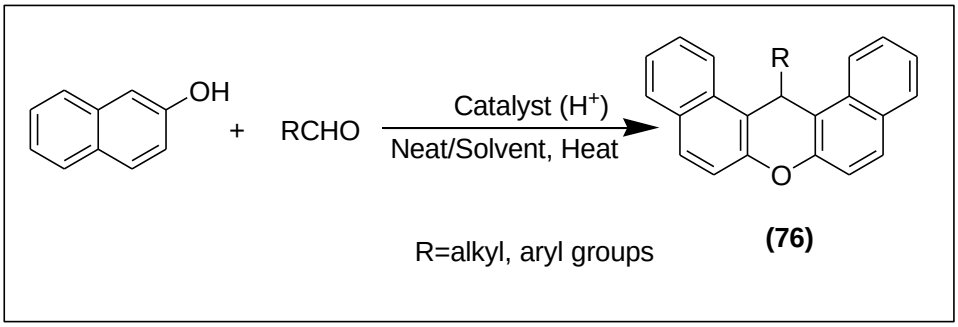


Scheme-41: Synthesis of dibenzoacridine from Betti base

1.5. Review of ionic liquid mediated/catalyzed synthesis of 14-substituted-14*H*-dibenzo[a,j]xanthene and tetrahydrobenzo[a]-xanthene-11-one derivatives

1.5a. Synthesis of 14-substituted-14-*H*-dibenzo[a,j]xanthenes

The convenient method of 14-alkyl or aryl-14*H*-dibenzo[a,j]xanthene **(76)** synthesis involves from the cyclocondensation of 2-naphthol with aldehydes (**Scheme-42**) in presence of a variety of Brønsted or Lewis acid catalysts including HCl [298], H_2SO_4 [299], H_3PO_4 [300], $HClO_4$ [301], sulfamic acid [302], I_2 [303], *p*-TSA [304] etc. The problems of these methods are longer reaction times, organic solvent as reaction medium, corrosive and toxic non-reusable catalysts, side products formation, requirement of excess reagents/catalysts and high temperature reactions. Organic chemists have developed several modifications of this classical route to overcome these limitations with the use of heterogeneous catalysts [305], acidic ionic liquids [306], aqueous medium [307], solvent-free thermal method [308], microwave energy [309] and ultra-sonication [310]. This part of this review has included the literature of ionic liquid mediated/catalyzed synthesis of dibenzoxanthene derivatives till 2014.



Scheme-42: General method of preparation of dibenzoxanthene derivatives

In 2008 Kantevari *et al* exploited the applications of 10 mol% of tetra-n-butyl ammonium bromide (TBAB) as molten ionic salt at 125 °C for 60-90 min to afford the 14-aryl-14*H*-dibenzoxanthene derivatives in 81-96% yields according to the classical two component reaction (**Scheme-42**) [311]. In microwave method, the same reaction was conducted at 130 °C for 4-6 min to get 78-95% of product. The catalyst was also reused up to 10^{th} cycle of reaction.

Chauhan and his group in 2008 reported an efficient, simple, and rapid synthesis of 14-alkyl- or aryl-14*H*-dibenzo[a,j]xanthenes in 1-(4-sulfonylbutyl)-3-methylimidazolium-*p*-toluenesulfonate and 1-(4-sulfonylbutyl)-3-methylimidazolium trifluoromethanesulfonate acidic ILs (**Fig.34**) at 125 °C for 10-30 min to produce 68-94% of product by the one-pot condensation of 2-naphthol with alkyl or aryl aldehydes [306].

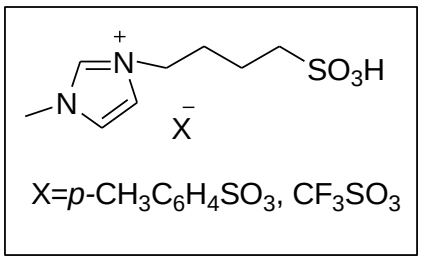


Fig.34: 1-(4-sulfonylbutyl)-3-methylimidazolium cation containing ILs

Wu *et al* in 2009 developed an efficient protocol of 14-aryl or alkyl-14*H*-dibenzo[a,j] xanthenes preparation using 0.08 mol% of 2-1´-methylimidazolium-3-yl-1-ethylsulfate ionic liquid (**Fig.35**) as catalyst at 80 °C for 5-8 hour to form 86-92 % yield of dibenzoxanthene derivatives [312]. The luminescence property of products was also studied in detail in this report.

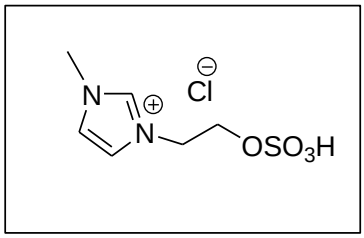


Fig.35: Structure of 2-1´-methylimidazolium-3-yl-1-ethylsulfate ionic liquid

In 2009, Liu *et al* examined the catalytic activity of three task specific Brønsted-acidic ILs [MIMPS][HSO_4], [MIMPS][H_2PO_4] and [MIMPS][BF_4] (**Fig.36**) for the preparation of 14-aryl or alkyl-14*H*-dibenzo[a,j]xanthene using 0.25 mmol of IL against 5 mmol of benzaldehyde and 10 mmol of 2-naphthol at 100 °C. Out of these three catalysts, only 1-methyl-3-propane sulfonic-imidazolium hydrosulfate [MIMPS][HSO_4] IL catalyzed the reaction with aromatic or aliphatic aldehydes within 5-60 min to generate 75-96 % of dibenzoxanthene derivatives [313].

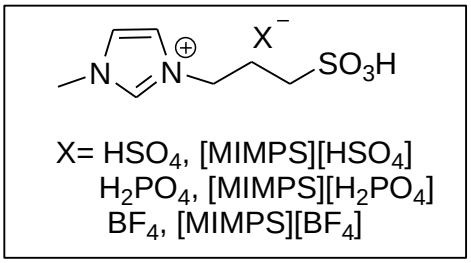


Fig.36: Sulfonic acid functionalized ionic liquid catalysts

This method offered the advantages of high yield, short reaction time, recycle of catalyst, simplicity and easy workup compared to the conventional method of synthesis.

Fang *et al* (2010) utilized some recyclable acyclic SO_3H-functionalized ionic liquids (**Fig.37**) as catalysts for the synthesis of 14-aryl-14*H*-dibenzo[a,j]xanthenes via the one-pot condensation of 2-naphthol and aromatic aldehydes in aqueous medium. The condensation reaction was performed successfully with various aromatic aldehydes with good to excellent yields (86- 96%) within 5-30 min. After completion of the reaction, the products could simply be separated from the catalysts by filtration [314].

In 2010, Rahmati *et al* synthesized various 14-alkyl or aryl dibenzoxanthenes from aliphatic or aromatic various aldehydes using trifluoroacetic acid as catalyst in 1,1,3,3-N,N,N´,N´-tetramethylguanidinium trifluoroacetate (TMGT) ionic liquid within 1 h at 75 °C to afford 86-98 % of product [315].

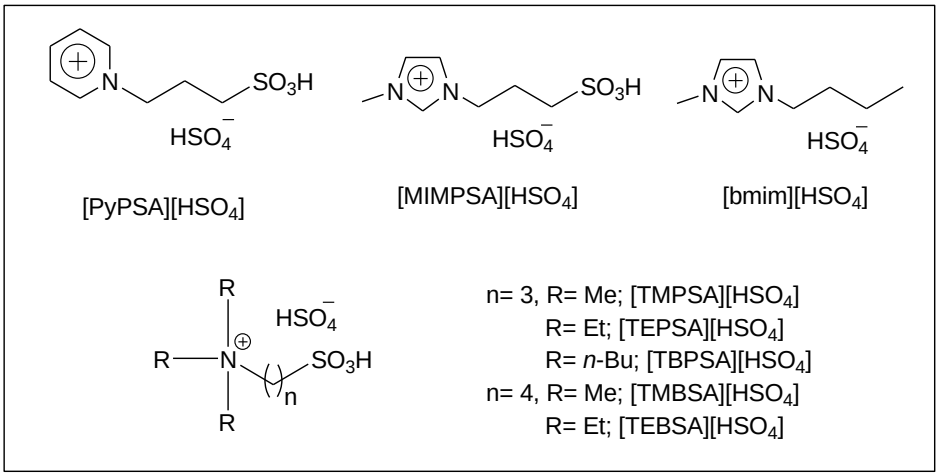
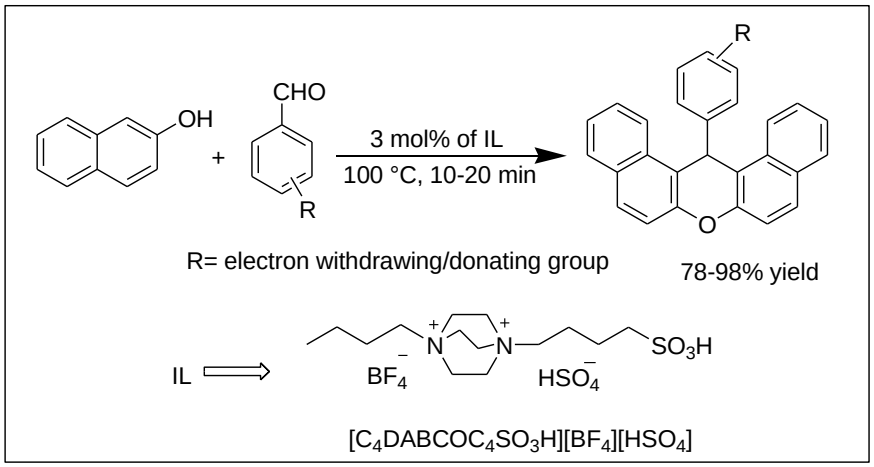


Fig.37: Brønsted acidic task-specific ionic liquids (TSILs) for dibenzoxanthene synthesis

Heravi *et al* (2011) prepared a new water stable Brønsted acidic pyridinium ionic liquid based on Keggin heteropoly acid ($H_3PW_{12}O_{40}$) and used as an environmentally benign catalytic medium in the synthesis of 14-aryl-14*H*-dibenzo[a,j]xanthenes at 90 °C for 3-14 min reaction with excellent results (87-98%). The catalyst can be easily recovered and reused without appreciable loss of activity [316].

Khazdooz *et al* in 2011 applied [Hmim][HSO_4] as Brönsted acidic ionic liquid catalyst for the preparation of 14-aryl or alkyl-14*H*-dibenzo[*a,j*]xanthenes at 125 °C for 0.5-4 h to produce good to moderate yields (62-92%) [317].



Scheme-43: Synthetic route of dibenzoxanthene reported by Davoondnia and his group

Davoodnia and his co-worker in 2012 have (**Scheme-43**) utilized only 3 mol% of 1-butyl-4-(4-sulfonylbutyl)-1,4-diazoniabicyclo[2.2.2]octanehydrogensulfate-tetrafluoroborate [$C_4DABCOC_4SO_3H$][BF_4][HSO_4] IL as catalyst for the synthesis of 78-95 % of 14-aryl-

14*H*-dibenzo[a,j]xanthenes at 100 °C during 10-20 min. It was reused for three times with slight reduction in its catalytic activity. [188]

Roohandeh and his group in 2012 *et al* used only 15 mol% of triethylamine bonded sulfonic acid [$Et_3N–SO_3H$][Cl] as homogeneous reusable IL catalyst for the synthesis of 14-aryl-14*H*-dibenzo[a,j]xanthenes from β-naphthol (2 equiv) and aldehydes (1 equiv) at 120 °C in neat condition during 15-40 min with excellent yields of product [318].

Azimi and his co-worker (2012) employed a recyclable homogeneous ionic liquid-catalyst system made up of 0.5 mol% $Mg(BF_4)_2$ doped in 3-butyl-1-methylimidazolium-tetrafluoroborate IL for the synthesis of 14-aryl-14*H*-dibenzo[a,j]xanthenes with 84-98% of yield under solvent-free method at 80 °C within 15-30 min [277].

Zolfigol *et al* (2012) also studied the same reaction using 10 mol% of 3-methyl-1-sulfonic acid imidazolium based ILs [Msim][X] (where X= Cl, PF_6 and BF_4) as reusable catalyst to produce excellent yields of 14-aryl-14*H*-dibenzoxanthene derivatives at 110 °C within 3-18 min under solvent less medium [319].

Zhou *et al* (2013) used [Et_3NH][HSO_4] as reusable acidic IL catalyst to prepare 77-93 % of 14-aryl-14-*H*-dibenzoxanthene derivatives at 120 °C for 20-120 min in solvent-free condition [320].

In 2013, Naeimi *et al* carried out the classical one-pot preparation of 14-aryl-14*H*-dibenzo[a,j]xanthenes using 20 mol% of acyclic Brønsted acidic IL, [H–NMP][HSO_4] **(Fig.38)** under 450 W microwave power in ethanol for 3-7 min to obtain 78-97 % yield. This acidic IL was prepared from the reaction of equimolar amount of 1-Methyl-2-pyrolidone with sulfuric acid at 80 °C for 12 hour [321]. They also studied the same reaction at 110 °C in absence of solvent for 10-25 min to get similar results [322].

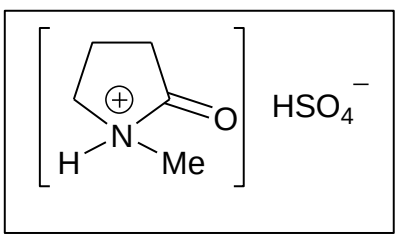


Fig.38: Structure of [H-NMP][HSO_4]

Moosavi-Zara *et al* in 2014 used 10 mol % of acetic acid functionalized imidazolium salts (1-carboxymethyl-3-methylimidazoliumbromide [cmmim][Br] or 1-carboxymethy1-3-methyl imidazolium tetrafluoroborate [cmmim][BF_4]) (**Fig.39)** as reusable catalysts at 115 °C for the formation of 83-95 % product of dibenzo[a,j]xanthenes within 15 to 30 min in neat condition [323].

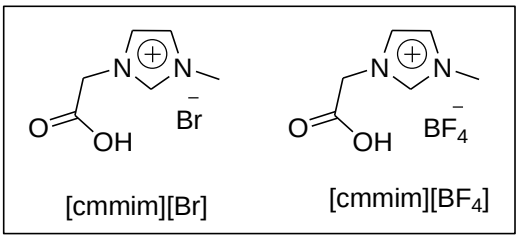
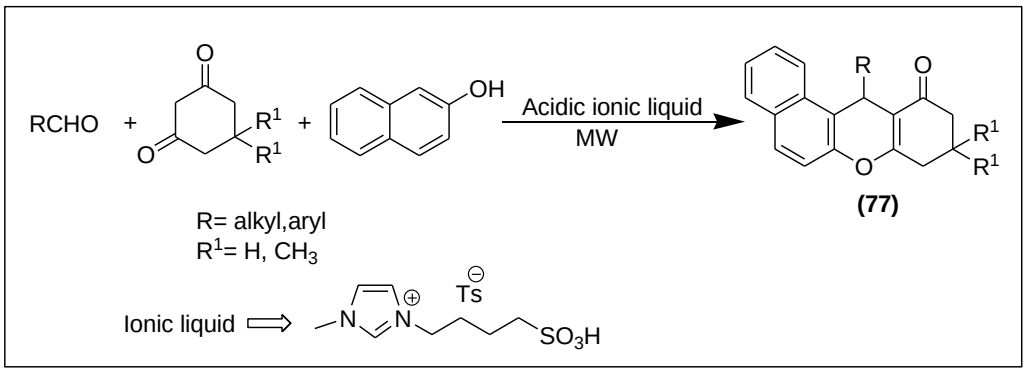


Fig.39: Acetic acid functionalized ILs for dibenzoxanthene synthesis

Recently Shirini *et al* (2014) again examined the catalytic activity of 1,3-disulfonic acid imidazolium hydrogen sulfate at 90 °C without any solvent for the one step reaction of 2-naphthol with various substituted aromatic aldehydes for 10 min to afford 84-95 % of dibenzoxanthene derivatives [324].

1.5b. Synthesis of tetrahydrobenzo[a]-xanthene-11-ones

Kundu *et al* in 2011, first explored the utility of 5 mol % of 1-butane sulfonic acid-3-methylimidazolium tosylate [BSMIM][Ts], as task specific reusable IL catalyst for the synthesis of 12-alkyl or aryl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-ones **(77)** by a three-component coupling of 2-naphthol, aldehydes, and cyclic 1,3-dicarbonyl compounds under solvent-free microwave irradiation (20 % microwave power) for 8-15 min to produce 70-89 % of required product (**Scheme-44**) [325].



Scheme-44: Synthesis of tetrahydrobenzo[a]-xanthene-11-one using [BSMIM][Ts]

In 2011, Masoumeh *et al* (2011) again investigated the catalytic activity of three Brønsted acidic ionic liquids such as 1-methylimidazolium hydrogen sulfate [HMIM][HSO_4], 1-(4-

sulfonic acid) butyl-3-methylimidazolium hydrogen sulfate[$(CH_2)_4SO_3HMIM][HSO_4$] and 1-(4-sulfonic acid) butylpyridinium hydrogen sulfate [PyBSA][HSO_4] (**Fig.40**) in neat condition at 120 °C for 1 hour using 10 mol % of each IL for the preparation 8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives **(77)**. Out of the three ILs, the catalytic performance of 1-(4-sulfonic acid) butyl-3-methylimidazolium hydrogen sulfate was efficient to form 70-95 % of product within 55-120 min reaction time. This IL was recycled for five runs under the optimized condition [326].

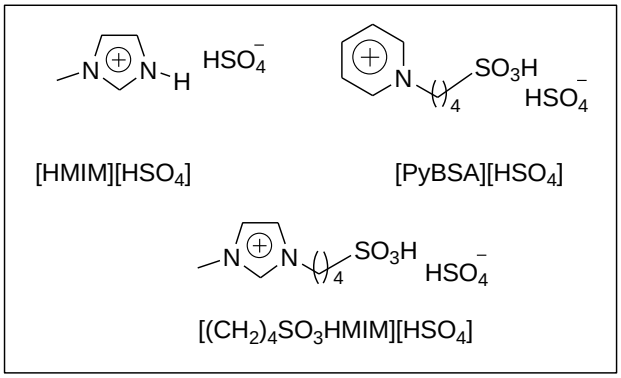
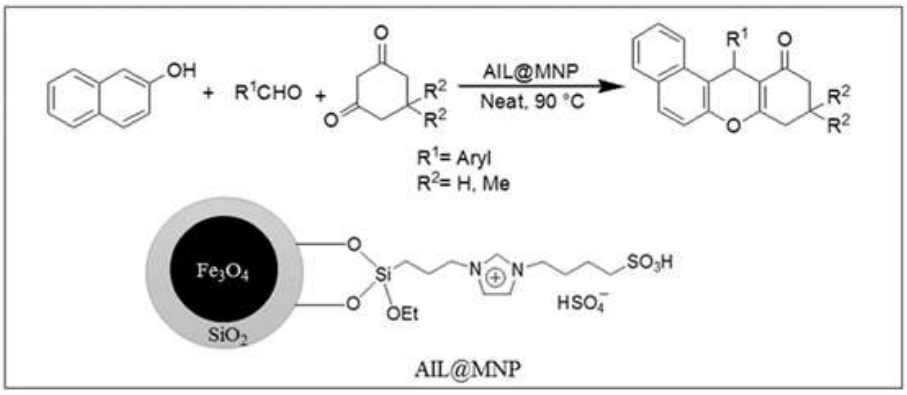


Fig.40: Brønsted acidic ionic liquids for the synthesis of tetrahydroxanthene

Zhang *et al* (2012) developed a magnetic nanoparticle supported dual acidic ionic liquid catalyst by anchoring 3-sulfobutyl-1-(3-propyltriethoxysilane) imidazolium hydrogen sulfate on to the surface of silica-coated Fe_3O_4 nanoparticles (AIL@MNP) **(Scheme-45)**. The combination of nano-support features and flexible imidazolium linkers acted as a "quasi-homogeneous" catalyst to effectively catalyze the one-pot synthesis of benzoxanthenes by a three-component condensation of dimedone with aldehyde and 2-naphthol under solvent-free conditions at 90 °C within 35-65 min to afford 80-95 % of product using 1.5 mol % catalyst. More importantly, the catalyst could be easily recovered by an external magnet and efficiently reused for six times without loss of catalytic activity [57].



Scheme-45: Synthesis of tetrahydrobenzo[a]xanthene catalyzed by AIL@MNP

Janardhan *et al* in 2012 used 10 mol % of (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogensulphate IL (**Fig.41**) as reusable catalyst for the preparation of 12-aryl tetrahydrobenzo[a]xanthene **(77)** at 80 °C within 15-45 min to get excellent results (88-98 % yields) [327].

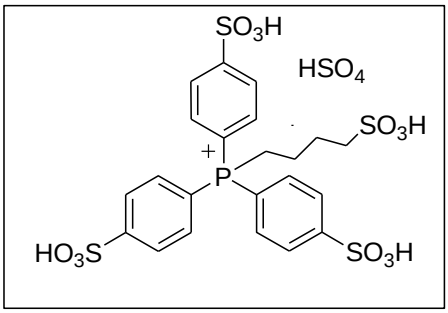


Fig.41: Structure of (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogen sulphate

The sulfamic acid catalysed solvent-free one-pot condensation of 2-naphthol, arylaldehyde and 5,5-dimethylcyclohexane-1,3-dione was performed in reusable 1-*n*-butyl-3-methylimidazolium tetrafluoroborate [BMIM][BF_4] ionic liquid at 80 °C for 2 hour to generate 76-88% of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives [328].

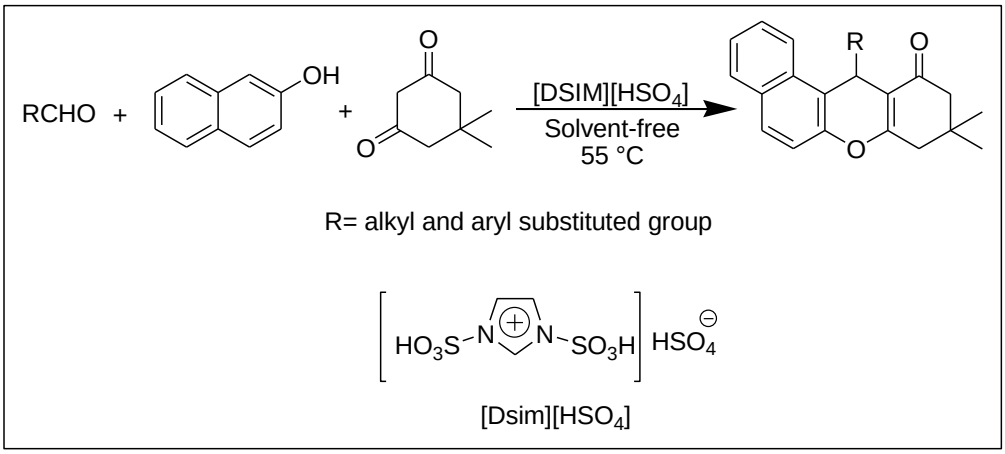
Hasaninejad and his group in 2012 explored the uses of 25 mol % of trimethylamine-bonded sulfonic acid [Et_3N-SO_3H][Cl] as reusable homogeneous catalyst for the formation of 78-94% yield of 12-aryl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-ones **(77)** from the reaction of 2-naphthol, dimedone and aromatic aldehydes in solvent-free condition at 120 °C for 30-60 min [329].

Zolfigol *et al* (2012) also tested the catalytic efficiency of the three sulfonic acid functionalised imidazolium ILs such as [Msim][Cl], [Msim][PF_6] and [Msim][BF_4] as reusable catalyst for the synthesis of 12-aryl-tetrahydrobenzo[a]-xanthene derivatives **(77)** that results more than 80 % of yields within the reaction time of 6-15 min at 110 °C [319].

The use of biodegradable acyclic -SO_3H functionalized ionic liquid catalyst [DDPA][HSO_4] was explored by Fang *et a*l in 2013 with 3 mol % of this IL as reusable catalyst for the synthesis of 85-93 % of 12-aryl- tetrahydrobenzo[a]xanthene derivatives **(77)** at 90 °C in absence of solvent for 30-60 min [169].

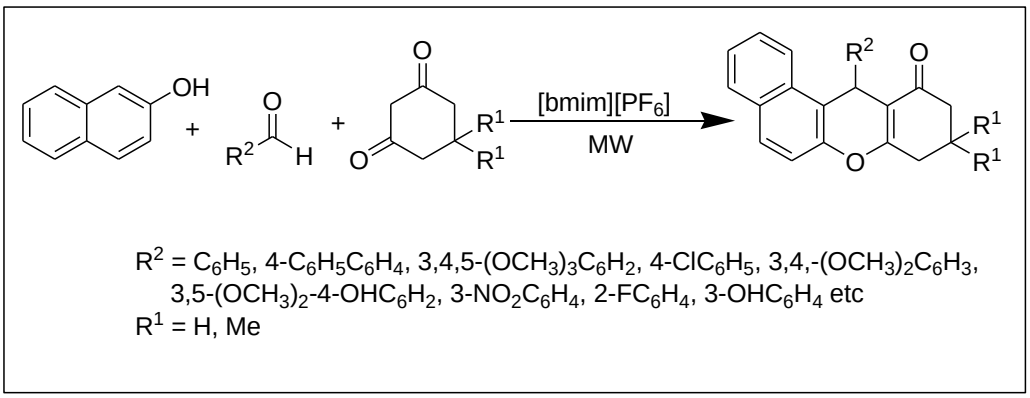
Khakyzadeh and his coworker (2013) used [Pyridine–SO_3H][Cl] as reusable catalyst for the synthesis of title compounds by condensation of various aromatic aldehydes, dimedone and 2-naphthol at 100 °C under solvent free condition. The results obtained were very good (85-96 % yield) for 7-15 min reaction time [195].

Shirini *et al* in 2014 studied 1, 3-disulfonic acid imidazolium hydrogen sulfate [DSIM][HSO_4] as an efficient and reusable ionic liquid for the green, mild, and efficient synthesis of tetrahydrobenzo[a]xanthenes under solvent-free conditions at 55 °C for 10-35 min to afford 87-93 % of product (**Scheme-46**) [324].



Scheme-46: [DSIM][HSO_4] catalyzed synthesis of tetrahydrobenzo[a]xanthene

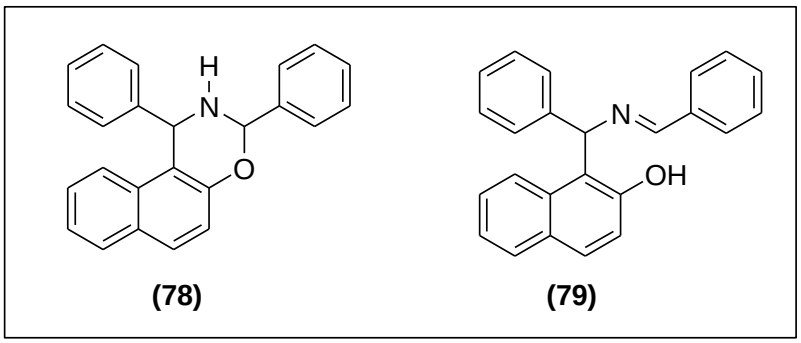
In 2014, Iniyavan *et al* reported microwave assisted synthesis of tetrahydrobenzo[a]-xanthene derivatives using 10 mol % of [bmim][PF_6] ionic liquid as reusable catalyst and yielded around 82-92 % of product within 12-17 min (**Scheme-47**) [330].



Scheme-47: [bmim][PF_6] catalyzed synthesis of tetrahydrobenzoxanthene

1.6. Literature review for one-pot synthesis of [1, 3]-naphthoxazine derivatives

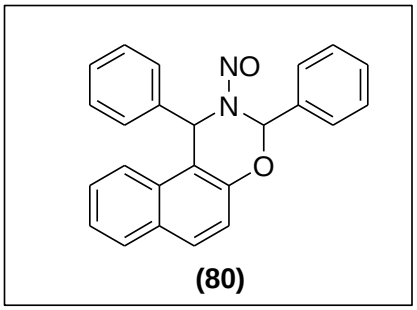
In 1901, Betti *et al* first assigned the structure of 1,3-diphenyl-2,3-dihydro-1*H*-naphth[1,2-e][1,3] oxazine as (**78) (Fig.42)** for the crystalline condensation product of 2-naphthol, benzaldehyde, and ammonia in a molar ratio of 1: 2: 1 in 95 % ethanol for several hour stirring at room temperature [331].



(78) **(79)**

Fig.42: Disubstituted naphthoxazine and Betti base derivatives

Based on its reaction in benzene with ethereal $FeCl_3$, the author proposed another isomeric Schiff base structure N-benzylidine-l-(α-aminobenzyl)-2-naphthol **(79) (Fig.42)** and he concluded that aliphatic aldehydes give 3-alkyl-l-phenyl-2,3-dihydro-1*H*-naphth[1,2-e][1,3]oxazines whereas aromatic aldehydes and aliphatic ketones give the Schiff bases [332].



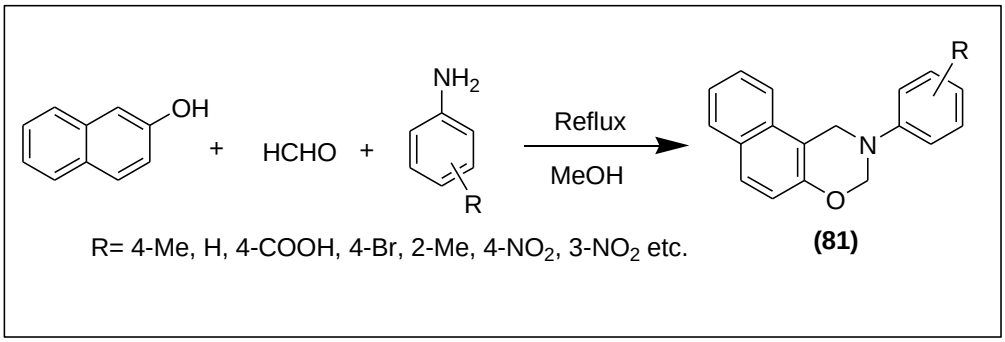
(80)

Fig.43: Naphthoxazine derivatives with N-nitroso group

Ahmed *et al* in 1934 observed that the condensation product of 2-naphthol, benzaldehyde, and ammonia when treated in ethyl ether with nitrous acid gives a compound N-nitroso-l,3-diphenyl-2,3-dihydro-1*H*-naphth[1,2-e][1,3]oxazine (**80**) (**Fig.43**). On this basis, the original condensation product was confirmed as structure **(78)** [333].

Bruke *et al* in 1954 explored the synthesis of 2,3-dihydro-2-aryl-l*H*-naphth[1,2-e]-m-oxazines **(81)** from a three component reaction of primary aryl amines, formaldehyde and

2-naphthol with molar ratio of 1:2:1 in hot methanol for several hour reaction and gave the product in the range of 27-91% yields **(Scheme-48)** [334]. They also described an alternate synthesis of the naphthoxazines through condensation of 1-arylaminomethyl-2-naphthols (**82)** [**Fig.44**] with formaldehyde in refluxing ethyl acetate for 2 hour.



Scheme-48: Synthesis of 2,3-dihydro-2-aryl-l*H*-naphth[1,2-e]-m-oxazines

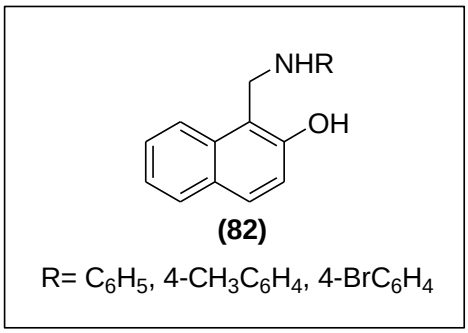


Fig.44: Structure of 1-arylaminomethyl-2-naphthols

Smith *et al* in 1970 also prepared a series of naphthoxazine derivatives **(83)** and **(84)** (**Fig.45**) by following the same procedure [331] in 95 % ethanol and confirmed that in crystalline state the infrared spectra of the condensation products of 1-(α-aminobenzyl)-2-naphthol with benzaldehyde and substituted benzaldehydes have the 2,3-dihydro-l*H*-naphth[1,2-e[**]**1,3]oxazine structure. The NMR spectra showed that in $CDCl_3$ they equilibrate to a mixture of diastereomers of the *cis*- **(83)** and *trans*- **(84)** naphthoxazine (ring) and the corresponding Schiff base (chain) tautomers **(85)**. The ring/chain ratio depends on the substituent in the benzaldehyde moiety which is greater in presence of strong electron-withdrawing group [335].

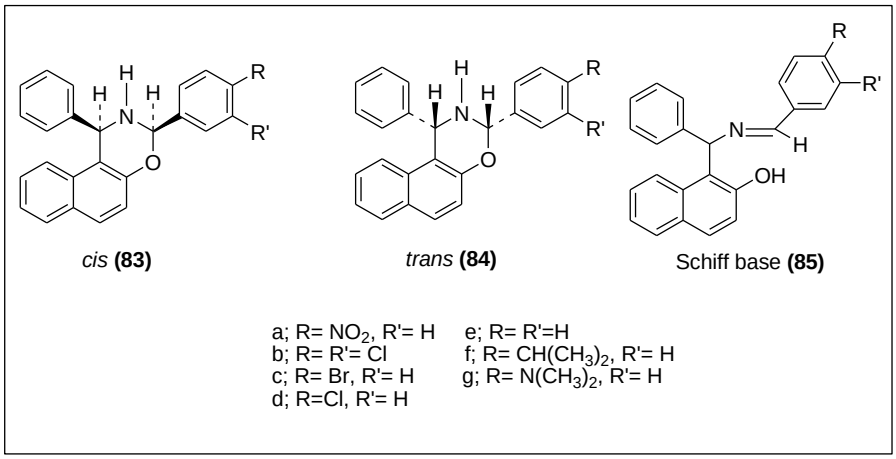
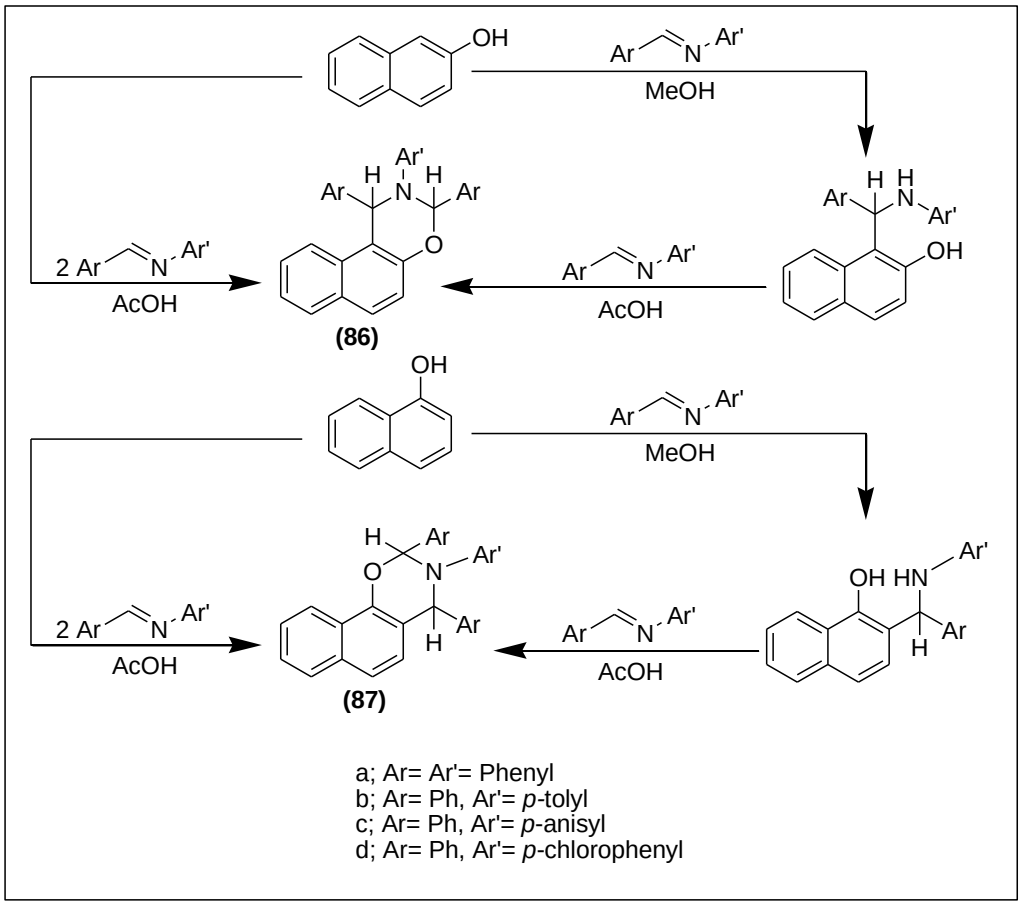


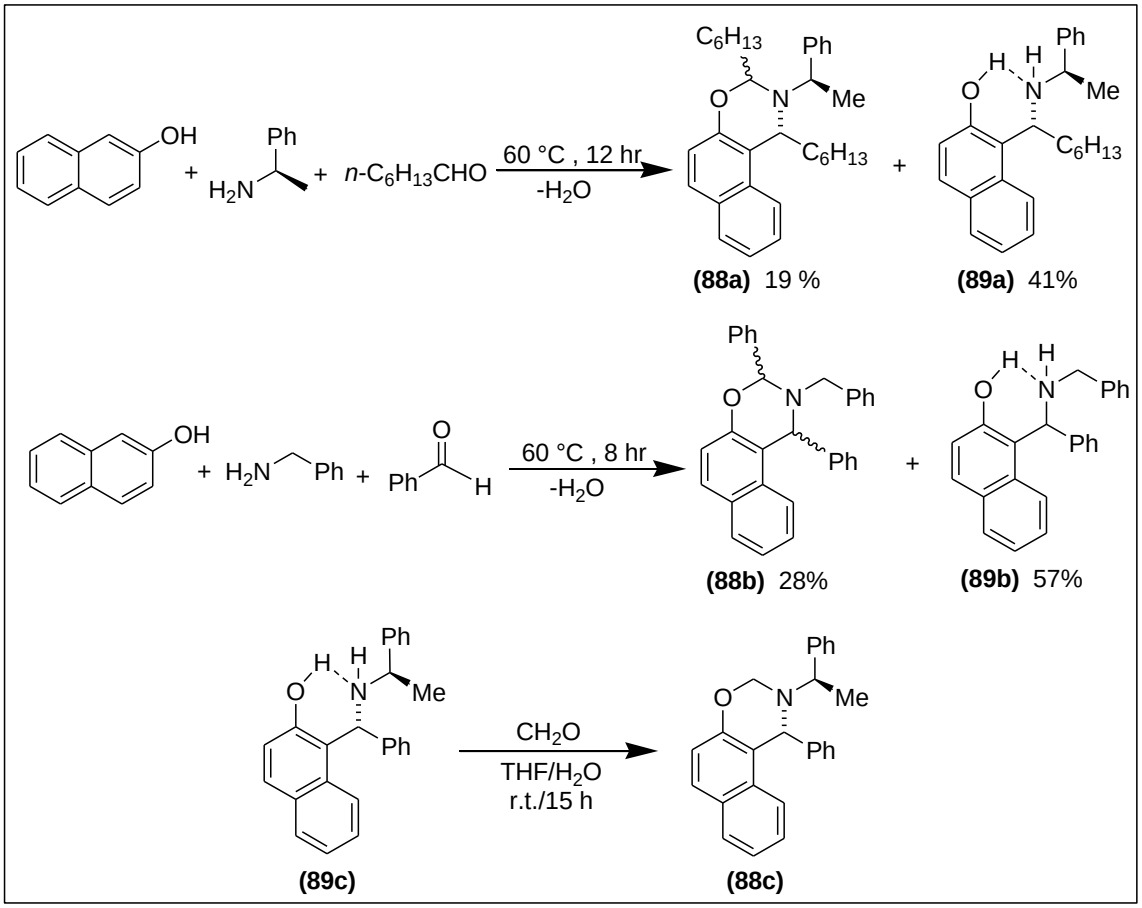
Fig.45: Tautomerism of *cis*- and *trans*-naphthoxazine



Scheme-49: Trisubstituted naphth[1,3]oxazine derivative from preformed Schiff bases

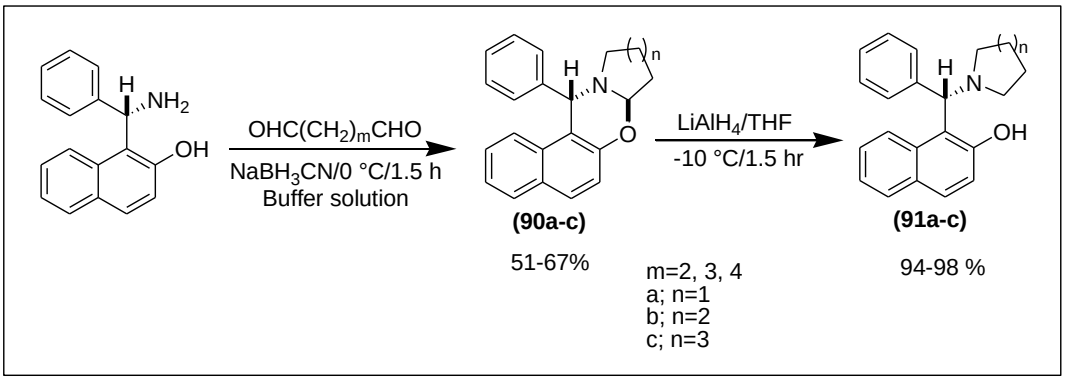
In 1977, Hanumanthu *et al* prepared few compounds of 2,3-dihydro-1,2,3-triaryl-1*H*-naphth[1,2-e][1,3]oxazines **(86)** and 3,4-dihydro-2,3,4-triaryl-2*H*-naph[2,1-e][1,3]oxazines **(87)** respectively from the condensation of 1-or 2-naphthol with preformed Schiff bases (benzylideneanilines) in AcOH at room temperature for several hours [336-337] (**Scheme-49).**

In 2001, Cimarelli *et al* isolated two derivatives of 2,3-dihydro-1,2,3-trisubtituted-1*H*-naphth[1,2-e][1,3]oxazines (**88a-b**) as side products during his enantioselective synthesis of aminoalkylnaphthols **(89a-b)** via three component reactions (**Scheme-50)** at 60 °C under N atmosphere for 8-12 hour. He also prepared chiral derivatives of 2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazine **(88c)** from a solution of enantiopure aminoalkylnaphthol (**89c)** in THF with 35 % aqueous formaldehyde for 15 h reaction at ambient temperature (**Scheme-50**) [338].



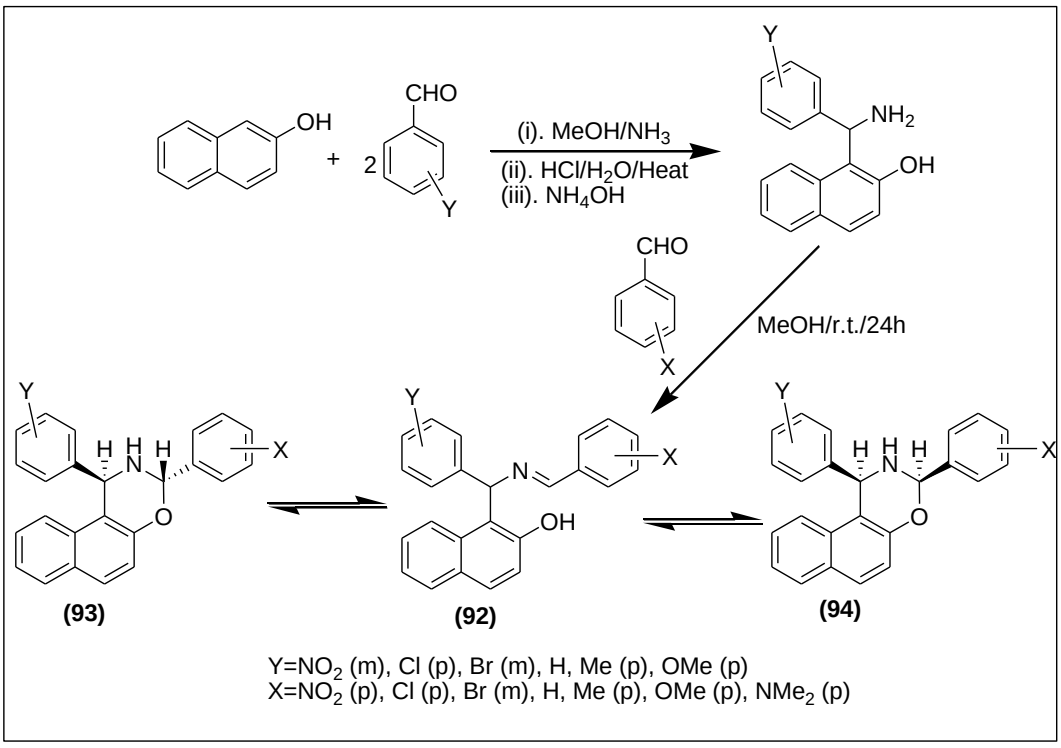
Scheme-50: Trisubstituted naphth[1,3]oxazines reported by Cimarelli *et al*

Lu *et al* (2002) isolated few chiral ring fused naphth[1,3]oxazine intermediate (**90a-c)** during the preparation of chiral Betti base ligands (S)-1-(cycloaminobenzyl)-2-naphthol (**91a-c)** by a suitable reaction of (S)-Betti base (**Scheme-51)** with 1, *n*-dialdehydes and $NaBH_3CN$ in an ethanol/buffer solution with 51-61 % yields [339].



Scheme-51: Synthesis of naphthoxazine from Betti base

Szatma´ri *et al* in 2003 studied the substituent effects in the ring-chain tautomerism of 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-e][1,3]oxazines (**93, 94**) which were obtained from the equivalent condensation of preformed Betti base analogue amino naphthols with substituted benzaldehydes in absolute methanol at room temperature for 24 hour (**Scheme-52**) and isolated as crystalline products within 67-93 % yields. The ^{1}H NMR spectra of these compounds revealed that, in $CDCl_3$ solution at 300 K, each of the compound participated in three-component ring chain tautomeric equilibria containing **C-3** epimeric naphthoxazines (**93, 94)** besides the open tautomer (**92)** except the equilibria of 3-(*p*-dimethylaminophenyl)-substituted derivatives contained only one ring-closed form (**16)** [340].



Scheme-52: Tautomeric equilibrium of naphthoxazines with Betti base

They also compared the effects of aryl substituents at 1-position on the tautomeric mixture of 1-unsubstituted 3-aryl-2,3-dihydro-1*H*-naphth[1,2-e][1,3] oxazines (**95**) derivatives [**Fig.46]**

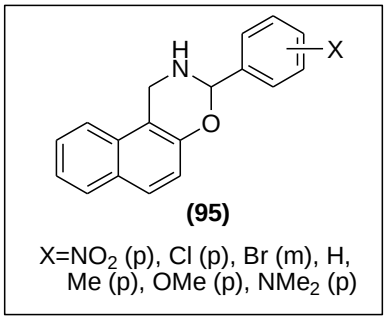
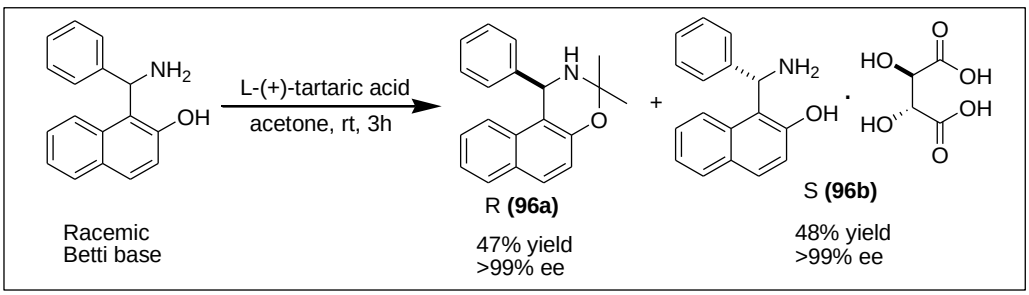


Fig.46: N-arylsubstituted naphthoxazine

Subsequently in 2004, the same group extended this study further for stereo electronic effects in ring-chain tautomerism of 1,3-diarylnaphth[1,2-e][1,3]oxazines and 3-alkyl-1-aryl-1*H*-naph[1,2-e][1,3]oxazines. Multiple linear regression analysis was used to analyse the di-substitution effects of X and Y in 1-(Y-phenyl)-3-(X-phenyl)-2,3-dihydro-1*H*-naphth[1,2-*e*]-[1,3]oxazines on the ring-chain tautomerism, the delocalization of the nitrogen lone pair (anomeric effect), and the ^{13}C NMR chemical shifts [341].

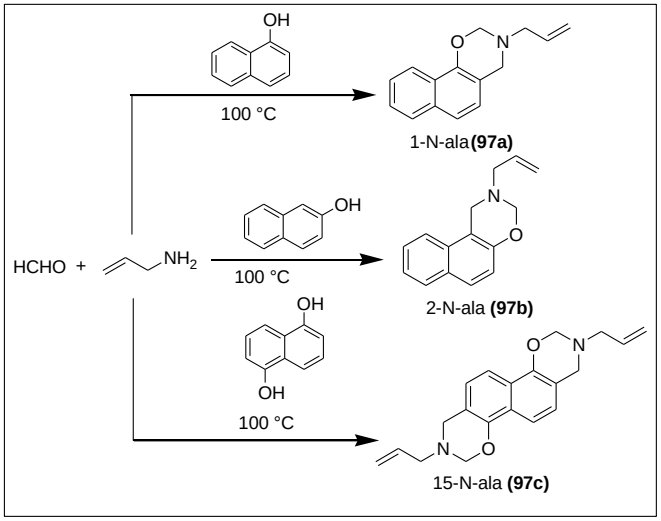
In 2005, Hu and his group developed an efficient kinetic resolution of racemic Betti base with L-(+)-tartaric acid in acetone based on enantioselective *N,O*-deketalization, by which the enantiopure *R*-and *S*-enantiomers of Betti base were obtained as the corresponding *N,O*-ketal compound **(96a)** and salt with L-(+)-tartaric acid **(96b)**, respectively, in excellent yields during 3 hour reaction at room temperature **(Scheme-53)** [342].



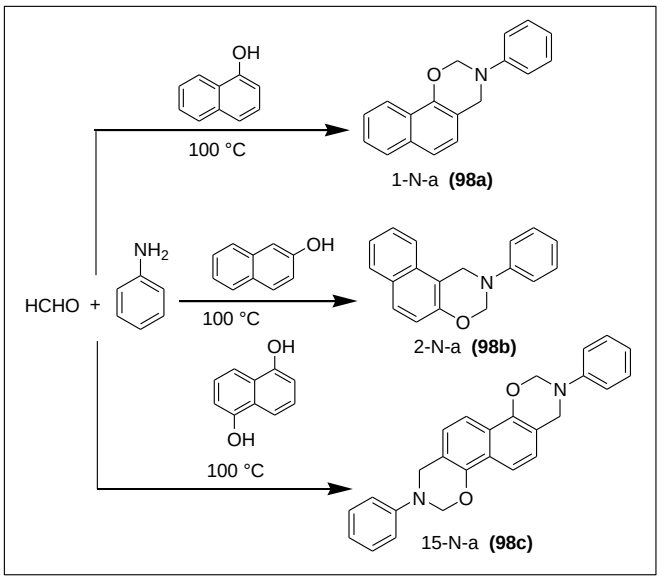
Scheme-53: Resolution of racemic Betti base

In 2006, Agag *et al* [343] prepared a series of novel naphthoxazine monomers containing allyl functionalities from the reaction of 1-naphthol, 2-naphthol, and 1,5-dihydroxynaphthalene with allylamine and formalin (**97a-c)** (**Scheme-54**). Another series of naphthoxazines were similarly prepared by using aniline instead of allylamine for

comparison (**98a-c)** (**Scheme-55**). The thermal cure of the allylamine-based naphthoxazine monomers gave thermoset resins with novel structure comprising of polynaphthoxazine with extended network via the polymerization of allyl functionalities.

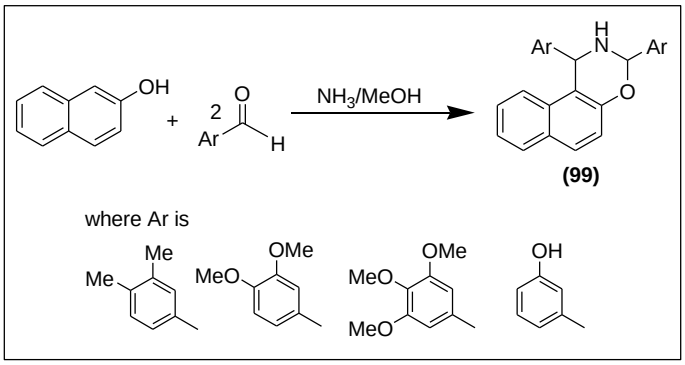


Scheme-54: Synthesis of allyl functionalized naphthoxazine monomers



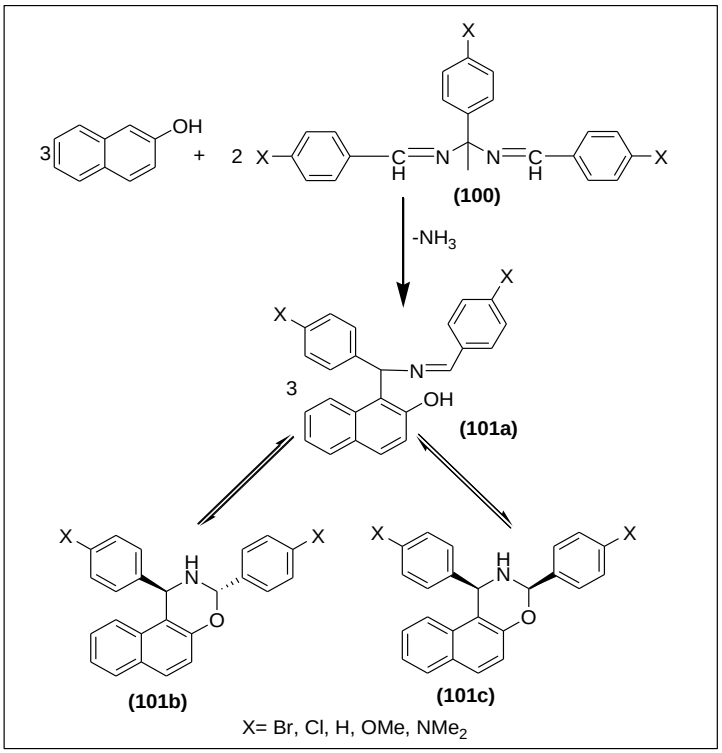
Scheme-55: Synthesis of naphthoxazine from aniline

In 2007, Turgut *et al* prepared some derivatives of 1,3-disubstituted-2,3-dihydro-1*H*-naphth[1,2-e][1,3]oxazines **(99)** through the ring-closure reactions of the aminobenzylnaphthols with substituted aryl and heteroaryl aldehydes by the three component reaction of one equivalent of 2-naphthol with two equivalent of aryl/heteroaryl aldehydes in 25 % methanolic ammonia solution at ambient temperature for 24-48 hour and resulted 52-61 % of naphthoxazine derivatives **(Scheme-56)** [344].



Scheme-56: Synthesis of 1,3-disubstituted naphthoxazines

In 2007, Zheltukhin *et al* discovered a new approach to the synthesis of 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-e][1,3]oxazines (**101b-c)**-Betti base derivatives (**101a)** by the interaction of 2-naphthol with very accessible 1,3,5-trisaryl-2,4-diazapenta-1,4-dienes **(100)** in molar ratio 3:2 in boiling benzene for 5-17 h and resulted excellent yields of (88-99 %) Schiff bases (**101a)** which exists in solution of $CDCl_3$ in tautomeric equilibrium of two diastereomeric *trans*- and *cis*-1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-e][1,3]oxazine structures (**101b)** and (**101c) (Scheme-57**) [345].



Scheme-57: Synthesis of naphthoxazines from 1,3,5-trisaryl-2,4-diazapenta-1,4-dienes

Li *et al* (2008) reported the monoclinic crystal structure of 2-butyl-1,3-diphenyl-2,3-dihydro-1*H*-naphth[1,2-e][1,3]oxazine **(102a)** (**Fig.47**) obtained from a three component

reaction of 2-naphthol, butylamine and benzaldehyde in the molar ratio of (1:1:2) in 95 % ethanol at room temperature stirring for 6 days [346]. Similarly Zhang *et al* (2009) also get another crystalline compound 2-benzyl-1,3-diphenyl-2,3-dihydro-1*H*-naphth[1,2-e][1,3]oxazine **(102b)** by the one-pot condensation of 2-naphthol, phenylmethanamine and benzaldehyde using the same molar ratio at 120 °C in absence of solvent under nitrogen atmosphere for 10 hour (**Fig.47**) [347] .

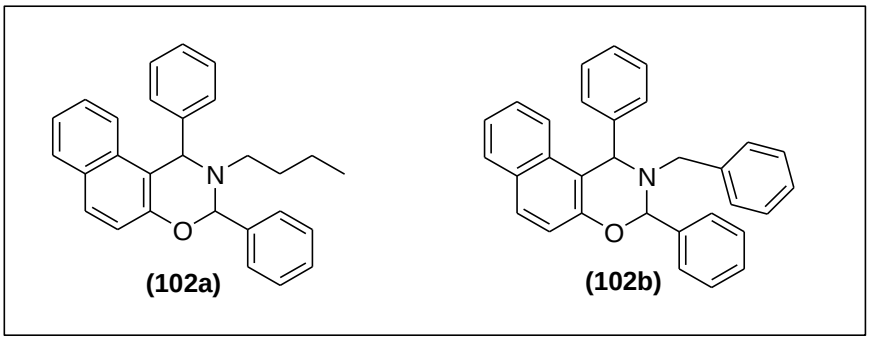
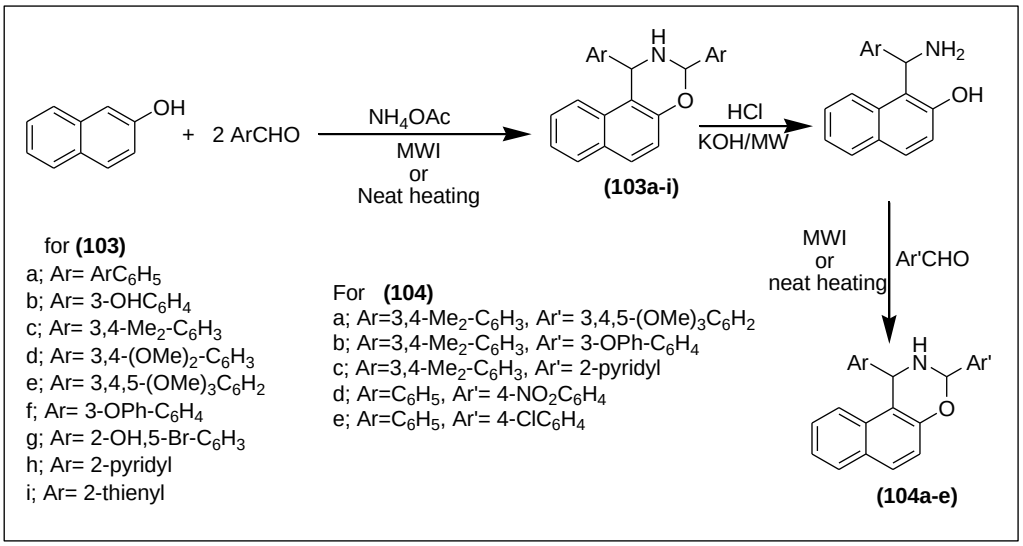


Fig.47: Structure of some crystalline naphthoxazine derivatives

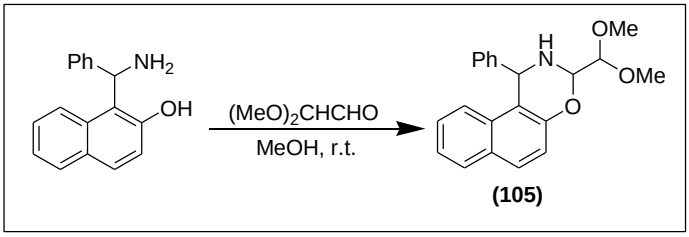


Scheme-58: Synthesis of disubstituted naphthoxazine under MWI

In 2009, Shingare and his group developed two methodology for the synthesis of 1,3-diaryl-2,3-dihydro-1*H*-naphth-[1,2e][1,3]oxazine (**103)** derivatives according to **Scheme-58** from the three component reaction of 2-naphthol, aromatic aldehyde and ammonium acetate in the molar ratio of 1:2:1 in neat at 60 °C and solvent-free microwave irradiation (360 W) with excellent yields (92-98%). The thermal method required more reaction time (25-40 min) as compared to that of the microwave assisted condition (7-15 min). They also prepared some 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2e][1,3]oxazine derivatives (**104)** containing two different substituted aryl groups by condensation of equimolar amount of

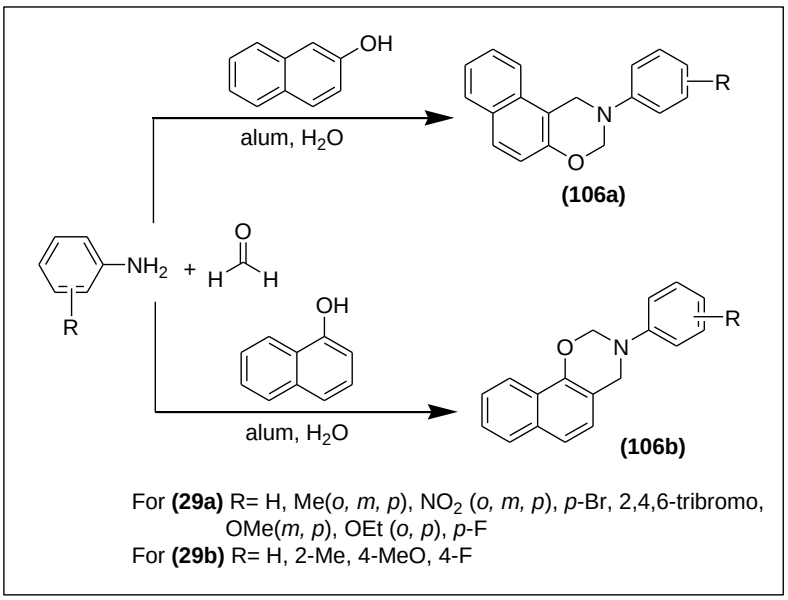
aminobenzylnaphthol and aromatic/heteroaromatic aldehydes at 60 °C for 25-40 min and under microwave energy (360 W) for 10-20 min in absence of solvent to afford 85-95 % of product. This protocol has provided several greener advantages by avoiding use of organic solvent as reaction medium, higher yields of product, shorter reaction time and simple isolation of product [348].

Hu and his group (2009) prepared N,O-acetal of 1,3-disubstituted naphth[1,3]oxazine **(105)** with 98 % yield by the ring closure reaction of Betti base with 2,2-dimethoxyacetaldehyde in methanol solution at room temperature **(Scheme-59)** [349].



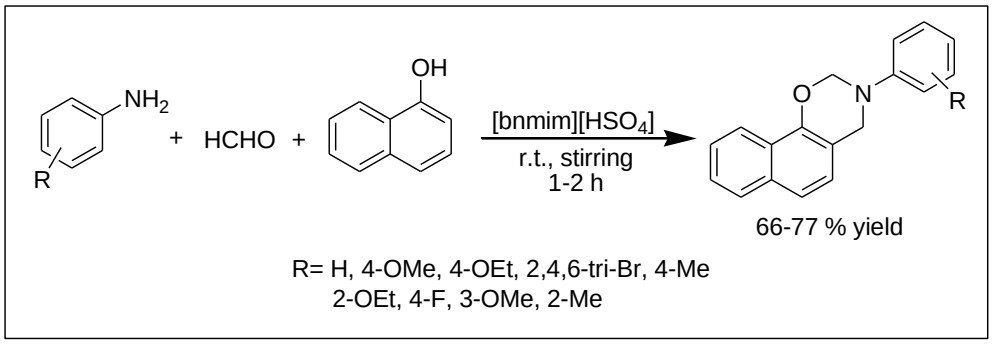
Scheme-59: Synthesis of N,O-acetal of 1,3-disubstituted naphth[1,3]oxazine

In 2010, the same group again utilized 20 mol% of $KAl(SO_4)_2.12H_2O$ (alum) as safe and reusable catalyst for the synthesis of various substituted 2,3-dihydro-2-phenyl-1*H*-naphth[1,2-e][1,3]oxazines (**106a)** and 3,4-dihydro-3-phenyl-2*H*-naphth[2,1-e][1,3]oxazines **(106b)** in water at room temperature for 10-25 min to produce 72-90 % of both the products **(Scheme-60).** These improved reaction conditions allow the preparation of a wide variety of substituted [1,3]oxazines in high yields and purity under mild reaction conditions [350].



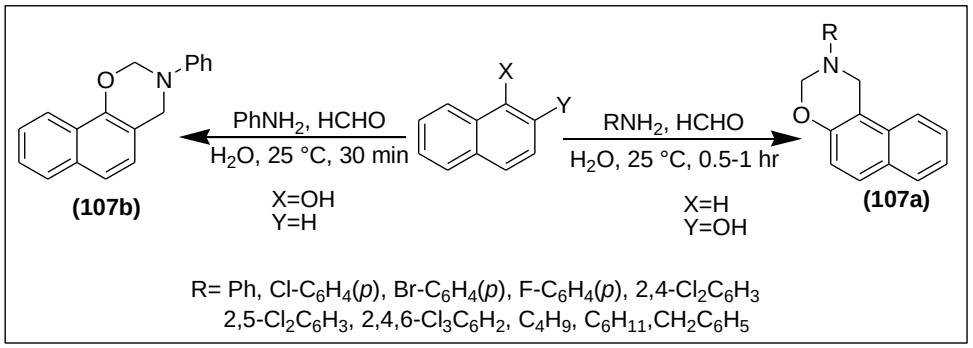
Scheme-60: Alum catalysed synthesis of N-aryl substituted naphth[1,3]oxazine

The same group also performed the synthesis of 3,4-dihydro-3-substituted-2*H*-naphth[2,1-*e*][1,3]oxazine derivatives from 1-naphthol, various anilines and formalin at room temperature stirring using 40 mol % of acidic reusable 1-benzyl-3-methyl imidazolium hydrogen sulphate [bnmim][HSO_4] ionic liquids within 1-2 hour reaction to afford 66-77 % yields (**Scheme-61**) [351].



Scheme-61: Synthesis of naphthoxazine catalysed by [bnmim][HSO_4]

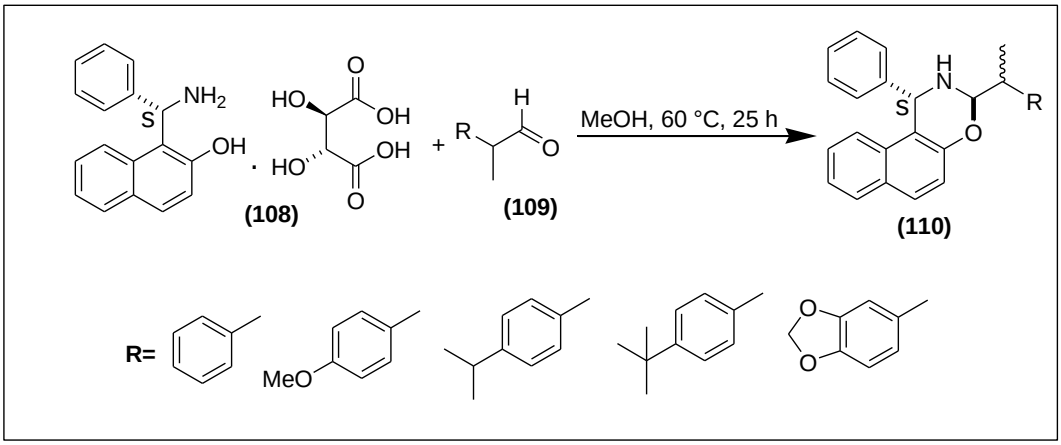
Methewa *et al* (2010) synthesized 2,3-dihydro-1*H*-naphth[1,2-e][1,3]oxazine (**107a)** and 3,4-dihydro-2*H*-naphth[2,1-e][1,3]oxazines (**107b)** by an eco-friendly Mannich type condensation–cyclization reaction of 1-naphthol or 2-naphthol with 37 % formaldehyde solution and primary aliphatic or aromatic amines in water at ambient temperature within 0.5-1 hour (**Scheme-62**). Preliminary in vitro antimicrobial activity of the synthesized compounds was assessed against six pathogenic fungi, two Gram-negative and two Gram-positive bacteria. Some of the screened compounds have shown significant in vitro antimicrobial effect [352].



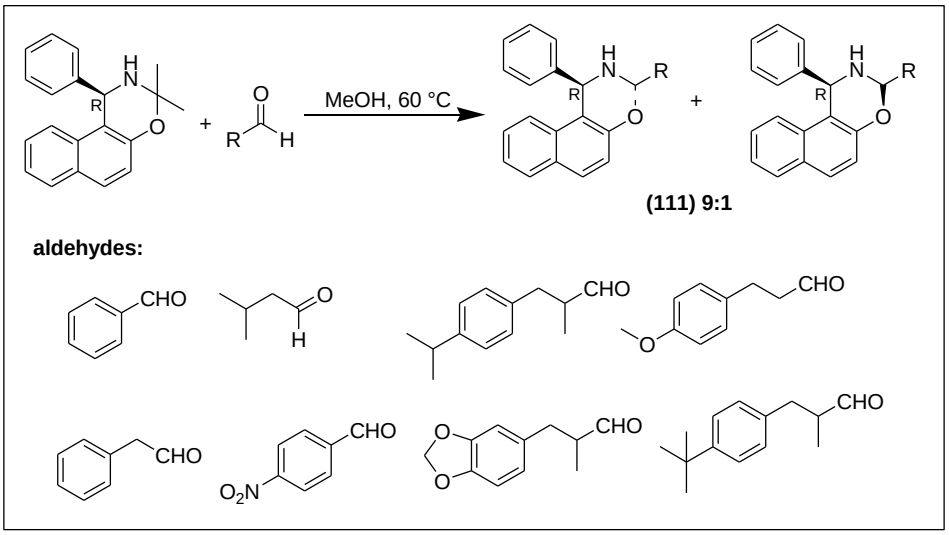
S**cheme-62:** Synthesis of N-alkyl or aryl substituted naphthoxazine in water

Paolucci and his co-workers (2014) developed an improved procedure for direct use of L-(+)-tartaric acid salt of (S)-enantiomer of Betti base **(108)** by treating with various racemic α-alkyldihydrocinnamic aldehydes (2-alkyl-3-phenylpropanals) (**109)** in MeOH at 60 °C during 25 hour reaction for the synthesis of (S)-naphthoxazines (**110)** with diastereomeric

ratio enrichment (**Scheme-63**). The preparation of isomeric (R)-naphthoxazines (**111) (**9:1) were accomplished via transacetalization starting from N,O-ketal of *R*-enantiomer in a simple, green method (**Scheme-64)** [353].



Scheme-63: Synthesis of chiral (*S)*-naphthoxazine **(110)** using α-alkyldihydrocinnamic aldehydes



Scheme-64: Preparation of (*R)*-naphthoxazine **(111)** via transacetalization

An efficient and convenient synthesis of naphth[1,3]oxazine derivatives (**113a-b)** was achieved by Dhakane *et al* (2013) from the one-pot three-component condensation of 1-or 2-naphthol, substituted aniline and formaldehyde using thiamine hydrochloride (VB_1) **(112)** as a versatile biodegradable and reusable catalyst in water within 20-45 min to generate 75-92 % yields **(Fig.48)** [354].

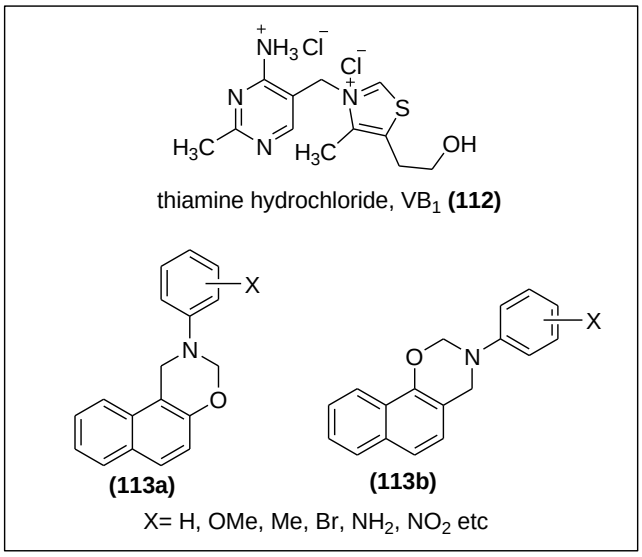
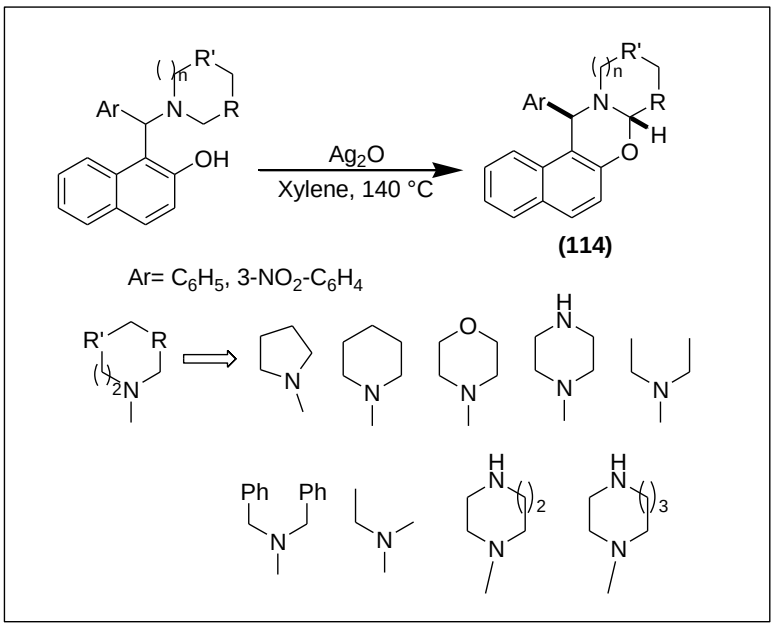


Fig.48: Structure of thiamine hydrochloride (VB_1) and some naphth[1,3]oxazine derivatives

In 2014 Jana and his group [355] developed a method to prepare a diverse ring fused naphthoxazine (**114)** derivatives via alpha C–H aryloxylation of aliphatic amines of various Betti bases in presence of Ag_2O under reflux in *m*-xylene at 140 °C for several hour to produce moderate to good yields of ring fused naphthoxazine derivatives (**Scheme-65**). The different Betti bases were prepared from the three component reactions of 2-naphthol, aromatic aldehydes and saturated secondary amines by known procedure [331]. The method is efficient in functionalizing broad classes of both cyclic and acyclic amines including the substrates that are otherwise difficult to functionalize. It produces highly diastereoselective oxazines.



Scheme-65: Ag_2O catalysed synthesis of naphthoxazine

References

[1] Joule, J.A. & Mills, K. *Heterocyclic Chemistry,* 5th Ed., John Wiley & Sons, Ltd. Publications, 2010.

[2] Blackburn, G.M. & Gait, M.J. *Nucleic Acids in Chemistry and Biology,* Oxford University Press, 1996.

[3] Cordell, G.A. *The Alkaloids: Chemistry and Biology,* Elsevier, and previous volumes of the series, 2010.

[4] Katritzky, A.R. & Rees, C.W. *Comprehensive Heterocyclic Chemistry*, Pergamon Press: New York, 1984.

[5] Katritzky, A.R., Ress, C.W. & Scriven, E.F.V. *Eds. Comprehensive Heterocyclic Chemistry,* 2nd ed., Pergamon, New York, 1996.

[6] Balaban, A.T., et al. *Chem. Rev.* **104**, 2777--2812, 2004.

[7] Martins, M.A.P., et al. *Curr. Org. Synth.* **1**, 391--403, 2004.

[8] Martins, M.A.P., et al. *Chem. Rev.* **108**, 2015--2050, 2008.

[9] Ghosh, A.K., et al. *J. Comb. Chem.* **1**, 55--68, 1999.

[10] Xu, J., & Stevenson, J. *J. Chem. Inf. Comput. Sci.* **40**, 1177--1187, 2000.

[11] Allard, N., et al. *Macromolecules,* **43**, 2328--2333, 2010.

[12] Hu, J., et al. *ACS Macro Lett.* **4**, 236--241, 2015.

[13] Herrmann, W.A. *Angew. Chem. Int. Ed.* **41**, 1290--1309, 2002.

[14] Shi, X., et al. *Inorg. Chem.* **46,** 7944--7952, 2007.

[15] Konev, A.S., et al. *Tetrahedron Lett.* **46**, 8337--8840, 2005.

[16] Minetto, G., et al. *Org. Lett.* **6**, 389--392, 2004.

[17] Janvier, P., et al. *J. Am. Chem. Soc.* **124**, 2560--2567, 2002.

[18] Yoon, S.C., et al. *J. Org. Chem.* **66**, 7334--7341, 2001.

[19] Kobayashi, J., et al. *Tetrahedron Lett.* **29**, 1177--1180, 1988.

[20] Chung, G.A.C., et al. *Antimicrob. Agents Chemother.* **39**, 2235--2238, 1995.

[21] Appleton, D.R., et al. *Tetrahedron* **66**, 4977--4986, 2010.

[22] Denny, W.A. *Curr. Med. Chem.* **9**, 1655--1665, 2002.

[23] Cholewiñski, G., et al. synthesis, *Pharmacol. Rep.* **63**, 305--336, 2011.

[24] Huang, L., et al. *Fitoterapia,* **81**, 389--392, 2010.

[25] Yang, D.M., et al. *Tetrahedron,* **29**, 519--528, 1973.

[26] Matsuzaki, K., et al. *Tetrahedron Lett.* **34**, 8251--8254, 1993.

[27] Uchida, I., et al. *J. Am. Chem. Soc.* **109**, 4108--4109, 1987.

[28] Wan, X., & Joullié, M.M. *Front. Chem. China,* **4,** 249--258, 2009.

[29] Liu, R., et al. *Arch. Pharm. Res.* **28**, 1042--1046, 2005.
[30] Garo, E., et al. *J. Nat. Prod.* **66**, 423--426, 2003.
[31] Davis, R.A., et al. *Bioorg. Med. Chem. Lett.* **18**, 2836--2839, 2008.
[32] Moya, P., et al. *J. Org. Chem*. **62**, 8544--8545, 1997.
[33] Ferlin, M.G., et al. *Eur. J. Med. Chem.* **35**, 827--837, 2000.
[34] Gamega, S.A., et al. *J. Med. Chem.* **42**, 2383--2393, 1999.
[35] Mikata, Y., et al. *Inorg. Chim. Acta,* **279**, 51--57, 1998.
[36] Ngadi, L., et al. *Eur. J. Med. Chem.* **25**, 67--70, 1990.
[37] Mannhold, R., et al. *Eur. J. Med. Chem.* **27**, 229--235, 1992.
[38] Wainwright, M. *J. Antimicrob. Chemother*. **47**, 1--13, 2001.
[39] Spalding, D.P., et al. *J. Org. Chem.* **19,** 357--364, 1954.
[40] Albert, A. *The acridines*, St. Martin's Press, New York, 1966.
[41] Greenwood, D. *J. Antimicrob. Chemother.* **36,** 857--872, 1995**.**
[42] Gniazdowski, M., & Szmigiero, L. *Gen. Pharmacol.-Vasc. S.* **26,** 473--481, 1995.
[43] Bossert, F., & Vater, W. *Med. Res. Rev*. **9**, 291--324, 1989.
[44] Alinezhad, H., et al. *Res. Chem. Intermed.* **41,** 9979--9992, 2015.
[45] Eisner, U., & Kutham, J. *Chem. Rev.* **72,** 1--42, 1972.
[46] Chorvat, R.J., & Rorig, K.J. *J. Org. Chem.* **53,** 5779--5781, 1988.
[47] Murugan, P., et al. *J. Chem. Soc. Perkin Trans. 2* 999--1004, 1998
[48] Islam, A., et al. *Synth. Met.* **139**, 347--353, 2003.
[49] Tu, S.J., et al. *Synlett* **2004**, 255--258, 2004.
[50] Sivaraman, J., et al. *J. Mol. Struct.* **385**, 129--135, 1996.
[51] Zhang, G., et al. *Synthesis* **2010**, 3993--3998, 2010.
[52] Benniston, A.C., & Rewinska, D.B. *Org. Biomol. Chem.* **4,** 3886--3888, 2006.
[53] Dadhania, A.N., et al. *C. R. Chim.* **15,** 378--383, 2012.
[54] Tayebee, R., & Tizabi, S. *Chin. J. Catal*. **33**, 962--969, 2012.
[55] Chibale, K., et al. *Tetrahedron* **59,** 2289--2296, 2003.
[56] Ion, R.M., et al. *ActaBiochim. Pol.* **45,** 833--845, 1998.
[57] Zhang, Q., et al. *Green Chem.* **14**, 201--208, 2012.
[58] Ahmad, M., et al. *J. Phys. D: Appl. Phys.* **35**, 1473--1476, 2002.
[59] Knight, C.G., & Stephens, T. *Biochem. J.* **258**, 683--687, 1989.
[60] Guedes, A.P., et al. *Phytochem. Rev.* **11,** 127--152, 2002.
[61] Zorzetto, C., et al. *Fitoterapia* **100**, 95–109, 2015.
[62] Martins, M.A.P., et al. *Chem. Rev.* **109**, 4140--4182, 2009.
[63] Zanatta, N., et al. *J. Braz. Chem. Soc.* **16,** 1255--1261, 2005.

[64] Testa, E., et al. *J. Org. Chem.* **24,** 1928--1936, 1959.
[65] Mueller, R., et al. *Bioorg. Med. Chem. Lett.* **21**, 3923--3926, 2011.
[66] Kupchan, S.M., et al. *J. Am. Chem. Soc.* **94**, 1354--1356, 1972.
[67] Mosher, H.S., et al. *J. Am. Chem. Soc.* **75**, 5326--5328, 1953.
[68] Zhang, P., et al. *Bioorg. Med. Chem. Lett.* **13,** 1313--1316, 2003.
[69] Adib, M., et al. *Tetrahedron* **62**, 3435--3438, 2006.
[70] Kerdesky, F.A.J. *Tetrahedron Lett*. **46**, 1711--1712, 2005.
[71] Joyce, J.N., et al. *Exp. Neurol.* **184**, 393--407, 2003.
[72] Feng, E., et al. *J. Org. Chem.* **75**, 3274--3282, 2010.
[73] Kurz, T. *Tetrahedron* **61**, 3091--3096, 2005.
[74] Shen, G., et al. *Tetrahedron* **68**, 166--172, 2012.
[75] Adib, M., et al. *Tetrahedron* **62**, 3435--3438, 2006.
[76] Tukulula, M., et al. *ACS Med. Chem. Lett.* **4**, 128--131, 2013.
[77] Anastas, P.T. & Warner J.C. *Green Chemistry: Theory and Practice,* Oxford University Press, Oxford, 1998.
[78] Anastas, P.T. & Williamson T.C. *Green Chemistry: Frontiers in Chemical Synthesis and Processes*, Oxford University Press, Oxford, 1998.
[79] Matlack, A.S. *Introduction to Green Chemistry*, Marcel Dekker, New York, 2001.
[80] Anastas, P.T. & Kirchhoff, M.M. *Acc. Chem. Res.* **35**, 686--694, 2002.
[81] Clark, J.H. *The chemistry of waste minimization,* Blackie, London, 1995.
[82] Constable, D.J.C., et al. *Green Chem.* **4**, 521--527, 2002.
[83] Curzons, A.D., et al. *Green Chem.* **3,** 1--6, 2001.
[84] Sheldon, R.A. & Bekkum H.V. *Fine chemicals through heterogeneous catalysis,* Wiley-VCH, Weinheim, 2001.
[85] Sheldon, R.A., & Downing, R.S. *Appl. Catal. A-Gen.* **189,** 163--183, 1999.
[86] Ichihashi, H., & Sato, H. *Appl. Catal. A-Gen.* **221**, 359--366, 2001.
[87] Tanaka, K., & Toda, F. *Chem. Rev.* **100**, 1025--1074, 2000.
[88] Toda, F. *Acc. Chem. Res.* **28**, 480--486, 1995.
[89] Nagendrappa, G. *Resonance*, **7**, 64--77, 2002.
[90] Reichardt, C. *Org. Process Res. Dev.* **11**, 105--113, 2007.
[91] Walsh, P.J., et al. *Chem. Rev.* **107**, 2503--2562, 2007.
[92] Cave, G.W.V., et al. *Chem. Commun.* **21**, 2159--2169, 2001.
[93] Kerton, F.M. *Alternative solvents for green chemistry*, The Royal Society of Chemistry, UK, 2009.
[94] Rothenberg, G., et al. *J. Am. Chem. Soc.* **123**, 8701--8708, 2001.

[95] Augustine, R.L. *Heterogeneous catalysis for the synthetic chemist,* Marcel Dekker, New York, 1996.

[96] Natale, I.M., & Helmy, A.K. *Clays Clay Miner.* **37,** 89--95, 1989.

[97] Bruggink, A., et al. *Org. Proc. Res. Dev.* **7,** 622--640, 2003.

[98] Lee, J.M., et al. *Chem. Soc. Rev.* **33**, 302--312 2004.

[99] Broadwater, S.J., et al. *Org. Biomol. Chem*. **3**, 2899--2906, 2005.

[100] Zhu, J. & Bienayme, H. *Multicomponent reactions*, Wiley-VCH, Weinheim, 2005.

[101] Bannwarth, W. & Felder, E. *Combinatorial chemistry,* Wiley-VCH, Weinheim, 2000.

[102] Toure, B.B., & Hall, D.G. *Chem. Rev.* **109**, 4439--4486, 2009.

[103] Ganem, B. *Acc. Chem. Res.* **42**, 463--472, 2009.

[104] D'Souza, D.M., & Mueller, T.J.J. *Chem. Soc. Rev.* **36**, 1095--1108, 2007.

[105] Bon, R.S., et al. *J. Org. Chem.* **70**, 3542--3553, 2005.

[106] Yu, J., et al. *Acc. Chem. Res.* **44**, 1156--1171, 2011.

[107] Eckert, H. *Molecules* **17**, 1074--1102, 2012.

[108] Sunderhaus, J.D., & Martin, S.F. *Chem. Eur. J.* **15**, 1300--1308, 2009.

[109] Ismabery, N., & Lavila, R. *Chem. Eur. J.* **14**, 8444--8454, 2008.

[110] Grondal, C., et al. *Nat. Chem.* **2**, 167–178, 2010.

[111] Strauss, C.R., & Trainor, R.W. *Aust. J. Chem.* **48**, 1665--1692, 1995.

[112] Strauss, C.R. *Aust. J. Chem*. **52**, 83--96, 1999.

[113] Roberts, B.A., & Strauss, C.R. *Acc. Chem. Res.* **38**, 653--661, 2005.

[114] Leadbeater, N.E. *Chem. Commun.* 2881--2902, 2005.

[115] Breslow, R., et al. *Tetrahedron Lett.* **24**, 1901--1904, 1983.

[116] Grieco, P.A., et al. *Tetrahedron Lett* .**24,** 1897--1900, 1983.

[117] Grieco, P.A., et al. *J. Org. Chem.* **48**, 3137--3139, 1983.

[118] Li, C.J. & Chan, T.H. *Organic Reactions in Aqueous Media,* Wiley, New York, 1997.

[119] Lindstrom, U. *Organic Reactions in Water*, Blackwell Publishing, Oxford, 2007.

[120] Li, C.J. *Chem. Rev.* **93**, 2023--2035, 1993.

[121] Li, C.J. & Chen, L. *Chem. Soc. Rev.* **35**, 68--82, 2006.

[122] Breslow, R. *Acc. Chem. Res.* **37**, 471--478, 2004.

[123] Pirrung, M.C. *Chem. Eur. J.* **12**, 1312--1317, 2006.

[124] Breslow, R. *Acc. Chem. Res.* **24,** 159--164, 1991.

[125] Blokzijl, W., & Engberts, J.B.F.N. *Angew. Chem., Int. Ed.* **32,** 1545--1579, 1993.

[126] Sijbren, O., & Engberts, J.B.F.N. *Org. Biomol. Chem.* **1**, 2809--2820, 2003.

[127] Lindstrom, U.M., & Andersson, F. *Angew. Chem., Int. Ed.* **45**, 548--551, 2006.

[128] Larsson, R. *Perspectives in Catalysis: In Commemoration of J. J. Berzelius*, CNK Gleerup, Sweden, 1981.

[129] Tanabe, K., & Hölderich, W. *Appl. Catal. A: General* **181,** 399--434, 1999.

[130] Zhang, Q., et al. *Green Chem.* **13**, 2619--2637, 2011.

[131] Keim, W. *Green Chem.* **5**, 105--111, 2003.

[132] Pons, J.M. & Santelli, M. *Lewis acids and selectivity in organic synthesis*, CRC Press, Boca Raton, 1996.

[133] Cheona, C.H. & Yamamoto, H. *Chem. Commun.* **47,** 3043--3056, 2011.

[134] Okuhara, T. *Chem. Rev.* **102,** 3641--3666, 2002.

[135] Fadhel, A.Z., et al. *Molecules* **15,** 8400--8424, 2010.

[136] Hamilton, D.J.C. *Science* **299,** 1702--1706, 2003.

[137] Welton, T. *Chem. Rev.* **248**, 2459--2477, 2004.

[138] Olivier, B.H., & Magna, L. *J. Mol. Catal. A: Chem.* **182-183**, 419--437, 2002.

[139] Corma, A., & Garcı´a, H. *Chem. Rev.* **103,** 4307--4365, 2003.

[140] Kaur, M., et al. *Chin. J. Chem.* **36,** 520--549, 2015.

[141] Sreekanth, P., et al. *Adv. Synth. Catal.* **345**, 936--938, 2003.

[142] Wasserscheid, P. & Welton, T. *Ionic liquids in synthesis*, Wiley-VCH, Stuttgart, 2002.

[143] Wasserscheid, P., & Keim, W. *Angew. Chem., Int. Ed.* **39**, 3773--3789, 2000.

[144] Pârvulescu, V.I., & Hardacre, C. *Chem. Rev.* **107**, 2615--2665, 2007.

[145] Chauhan, S.M.S., et al. *Tetrahedron* **61**, 1015--1060, 2005.

[146] Scott, J.L., et al. *Tetrahedron* **63**, 2363--2389, 2007.

[147] Calo, V., et al. *Eur. J. Org. Chem.* **17**, 3791--3802, 2006.

[148] Rogers, R.D. & Seddon, K.R. *Ionic Liquids III A: Fundamentals, Progress, Challenges, and Opportunities Properties and Structure,* American Chemical Society: Washington, 2005.

[149] Wilkes, J.S. *J. Mol. Catal. A: Chem.* **214**, 11--17, 2004.

[150] Kamal, A., & Chouhan, G. A *Tetrahedron Lett.* **46**, 1489--1491, 2005.

[151] Yadav, L.D.S., et al. *Tetrahedron Lett.* **48**, 7793--7795, 2007.

[152] Gui, J., et al. *Catal. Commun.* **5**, 473--477, 2004.

[153] Cole, A.C., et al. *J. Am. Chem. Soc.* **124,** 5962--5963, 2002.

[154] Forbes, D.C., & Weaver, *J. Mol. Catal. A: Chem.* **214**, 129--132, 2004.

[155] Gu, Y., et al. *Catal. Commun.* **4**, 597--601, 2003.

[156] Gu, Y., et al. *J. Mol. Catal. A: Chem.* **212**, 71--75, 2004.

[157] Akbari, J., & Heydari, *Tetrahedron Lett.* **50**, 4236--4238, 2009.
[158] Xing, H., et al. *Ind. Eng. Chem. Res.* **44,** 4147--4150, 2005.
[159] Xing, H., et al. *J. Mol. Catal. A: Chem.* **264**, 53--59, 2007.
[160] Fang, D., et al. *Ind. Eng. Chem. Res.* **45,** 7982--7984, 2006.
[161] Li, H., et al. *Catal. Commun.* **8**, 1759--1762, 2007.
[162] Li, X., & Eli, *J. Mol. Catal. A: Chem.* **279**, 159--164, 2008.
[163] Wang, Y., et al. *Catal. Commun.* **9**, 2475--2480, 2008.
[164] Cheng, G., et al. *Catal. Commun.* **10**, 201--204, 2008.
[165] Liu, S., et al. *Catal. Commun.* **9**, 2030--2034, 2008.
[166] Shen, W., et al. *J. Fluorine Chem.* **130**, 522--527, 2009.
[167] Zhao, Y., et al. *Catal. Commun.* **10**, 732--736, 2009.
[168] Dong, F., et al. *Catal. Commun.* **10**, 1267--1270, 2009.
[169] Fang, D., et al. *Res. Chem. Intermed.* **39**, 1745--1751, 2013.
[170] Leng, Y., et al. *Angew. Chem.* **121**, 174--177, 2009.
[171] Amarasekara, A.S., & Owereh, O.S. *Ind. Eng. Chem. Res.* **48**, 10152--10155, 2009.
[172] Amarasekara, A.S., & Wiredu, B. *Sustainable Energy* **2,** 102--107, 2014.
[173] Amarasekara, A.S., & Owereh, O.S. *Catal. Commun.* **11,** 1072--1075, 2010.
[174] Xu, D.-Q., et al. *Green Chem.* **11,** 1239--1246, 2009.
[175] Chen, Z., et al. *Tetrahedron Lett.* **52**, 2601--2604, 2011.
[176] Kore, R., & Srivastava, R. *J. Mol. Catal. A: Chem*. **345,** 117--126, 2011.
[177] Kore, R., & Srivastava, R. *Catal. Commun.* **12,** 1420--1424, 2011.
[178] Liu, X., et al. *Green Chem.* **13,** 697--701, 2011.
[179] Zolfigol, M.A., et al. *Appl. Catal. A-Gen.* **400,** 70--81, 2011
[180] Zolfigol, M.A., et al. *Org. Prep. Proced. Int.* **42,** 95--102, 2010.
[181] Zolfigol, M.A., et al. *J. Iran. Chem. Soc.* **7,** 646--651, 2010.
[182] Khazaei, A., et al. *Sci. Iran., Trans. C* **17,** 31--36, 2010.
[183] Zolfigol, M.A., et al. *Sci. Iran.* **19**, 1584--1590, 2012.
[184] Sajjadifar, S., et al. *Chem. Sci. Trans.* **3**, 292--302, 2014
[185] Khaligh, N.G. *J. Mo1. Catal. A*: *Chem*. **349**, 63--70, 2011.
[186] Shirini, F., et al. *J. Mol. Catal. A*: *Chem.* **365**, 15--23, 2012.
[187] Zare, A., et al. *J. Mol. Liq.* **178**, 113--121, 2013.
[188] Bidaki, A.Z., & Davoodnia, A. *Bull. Korean Chem. Soc.* **33**, 1154--1158, 2012.
[189] Khazaei, A., et al. *Sci. Iran. Trans. C* **18,** 1365--1371, 2012.
[190] Kraus, G.A., & Guney, T. *Green Chem.* **14,** 1593--1596, 2012.
[191] Karimi, B., & Vafaeezadeh, M. *Chem. Commun*. **48,** 3327--3329, 2012.

[192] Janardhan, B., et al. *J. Chem. Pharm. Res.* **4,** 519--525. 2012.

[193] Zare, A., et al. *Iran J. Catal.* **2,** 107--14, 2012

[194] Nemati, F., & Alizadeh, S.G. *J. Chem.* **2013,** 1--5, 2013.

[195] Zare, A.R.M., et al. *J. Mol. Liq.* **186**, 63--69, 2013.

[196] Eicher, T. & Hauptmann, S. *The Chemistry of Heterocycles. Structure, Reactions, Syntheses and Applications*, George Thieme Verlag, New York, 1995.

[197] Abraham, D.J. *Burgers Medicinal Chemistry and Drug Discovery,* 6th ed., John Wiley and Sons, New York, 2007.

[198] Bruce, F.C., et al. *J. Med. Chem.* **17**, 922--930, 1974.

[199] Acheson, R.M. *Introduction to the Chemistry of Heterocyclic Compounds* 3rd ed., Wiley Interscience, New York, 2008.

[200] Albert, A. *The Acridine*, St. Martin's Press, New York, 1966.

[201] Zhu, J. & Bienayme, H. *Multicomponent reactions*, Wiley-VCH, Weinheim, 2005.

[202] Shan, R., et al. *J. Med. Chem.* **47**, 254--261, 2004.

[203] Gooch, B.D., & Beal, P.A. *J. Am. Chem. Soc.* **126,** 10603--10610, 2004

[204] Stefanska, B., et al. *Bioorg. Med. Chem.* **13,** 1969--1975, 2005.

[205] Bouffier, L., et al. *J. Org. Chem.* **69**, 8144--8147, 2004.

[206] Chiron, J., & Galy, J. P. *Synthesis* **2004**, 313--325, 2004.

[207] Chen, H. *Chem. Res. Appl.* **12**, 164--168, 2000.

[208] Sivan, S., et al. *BioSystems* **70**, 21--33, 2003.

[209] Flock, S., et al. *J. Biomol. Struct. Dyn.* **11**, 881--900, 1994.

[210] Janis, R.A., et al. *Adv. Drug. Res.* **16,** 309--591, 1987.

[211] Delfourne, E., et al. *J. Org. Chem*. **65**, 5476--5479, 2000.

[212] Antonini, J., et al. *J. Med. Chem.* **44**, 3329--3333, 2001.

[213] Islam, A., et al. *Synth. Metals* **139,** 347--353, 2003.

[214] Cholody, W., et al. *J. Med. Chem.* **39,** 1028--1032, 1996.

[215] Murugan, P., et al. *J. Chem. Soc. Perkin Trans. 2* 999--1004, 1998

[216] Srividya, N., et al. *J. Org. Chem.* **61,** 5083--5089, 1996.

[217] Greenhill, J.V. *J. Chem. Soc. C* 2699--2703, 1971.

[218] Nikolaeva, T.G., et al. *Khim. Geterotsikl. Soedin.* **4**, 475--481, 2000.

[219] To, Q.H., et al. *Bull. Korean Chem. Soc.* **33**, 1170--1176, 2012.

[220] Vahdat, S.M., & Baghery, S. *Heterocycl. Lett.* **2**, 43--51, 2012.

[221] Ganesan, S.S., et al. *Lett. Org. Chem.* **11**, 682--687, 2014.

[222] Wang, X.-S., et al. *Chinese. J. Org. Chem.* **24,** 430--432, 2004.

[223] Das, B., et al. *J. Mol. Catal. A: Chem.* **247**, 233--239, 2006.

[224] Saeed, B., et al. *Chin. J. Chem.* **27**, 1953--1956, 2009.
[225] Chandrasekhar, S., et al. *Synthesis* **2008**, 1737--1740, 2008.
[226] Banerjee, B., & Brahmachari, G. *J. Chem. Res.* **38**, 745--750, 2014.
[227] Jin, T.-S., et al. *Synthesis* **2004**, 2001--2005, 2004.
[228] Niknam, K., et al. *J. Heterocyclic Chem.* **47,** 292--300, 2010.
[229] Rostamizadeh, S., et al. *J. Heterocyclic Chem.* **49**, 111--115, 2012.
[230] Ziarani, G.M., et al. *Arabian J. Chem.* **7**, 335--339, 2014.
[231] Martin, N., et al. *J. Heterocyclic Chem.* **32**, 235--238, 1995.
[232] Murugan, P., et al. *J. Chem. Soc., Perkin Trans. 2* 999--1004, 1998,
[233] Vanags, G., & Stankevich, E.I. *Zh. Obshch. Khim*. **30,** 3287--3290, 1960.
[234] Chaaban, I., et al. *J. Chem. Soc., Perkin Trans. 1* 1593--1596, 1979.
[235] Benny, J.C.N., et al. *Indian J. Heterocycl. Chem.* **4,** 145--146, 1994.
[236] Singh, K., et al. *Tetrahedron* **54,** 935--938, 1998.
[237] Shchekotikhin, Y.M., et al. *Chem. Heterocycl. Compd.* **37,** 1228--1233, 2001.
[238] Pyrko, A. N. *Chem. Heterocycl. Compd.* **39,** 1029--1031**,** 2003.
[239] Nadaraj, V., et al. *Indian J. Chem., Sect B* **46B,** 1703--1706, 2007.
[240] Li, J., et al. *Tetrahedron* **68**, 4138--4144, 2012.
[241] Tu, S.-J., et al. *Synth. Commun.* **32,** 2181--2185, 2002.
[242] Rezaei, R., et al. *Heterocycle. Commun.* **19,** 57--63, 2003.
[243] Kidwai, M., & Bhatnagar, D. *Chem. Pap.* **64**, 825--828, 2010.
[244] Li, Y.-L., et al. *J. Chem. Res.* **9**, 600--602, 2005.
[245] Ghorbani-Vaghei, R., & Malaekehpoor, S.M. *J. Iran. Chem. Soc*. **7,** 957--964, 2010.
[246] Davoodnia, A., et al. *Bull. Korean Chem. Soc.* **32**, 2243--2248, 2011.
[247] Davoodnia, A., et al. *Chin. J. Chem*. **33,** 1797--1801, 2012.
[248] Davoodnia, A., et al. *Synth. React. Inorg. M.* **44**, 70--78, 2014.
[249] Nakhi, A., et al. *Bioorg. Med. Chem. Lett.* **23**, 1828--1833, 2013.
[250] Mokhtary, M., et al. *Monatsh. Chem.* **145**, 1489--1494, 2014.
[251] Ramesh, K.B., & Pasha, M.A. *Bioorg. Med. Chem. Lett.* **24**, 3907--3913, 2014.
[252] Khodja, I.M., et al. *Synth. Commun.* **44**, 959--967, 2014.
[253] Mubarak, H.A.S.A.Y., et al. *Chem. Sci. Trans.* **3**, 819--825, 2014.
[254] Suárez, M., et al. *Heterocycles* **51**, 21--27, 1999.
[255] Tu, S.-J., et al. *Chin. J. Chem.* **20**, 703--706, 2002.
[256] Tu, S.-J., et al. *Synlett* **2004,** 0255--0258, 2004.
[257] Tu, S.-J., et al. *Synth. Commun.* **34**, 1289--1294, 2004.

[258] Nandagopal, S., et al. *Indian J. Chem. Sec B* **42B**, 3145--147, 2003.
[259] Ashry, E.S.H.E., et al. *Arkivoc* **2006,** 178--186, 2006.
[260] Muscia, G.C., et al. *Monatsh. Chem.* **140,** 1529--1532, 2009.
[261] Tang, Z.-Q., et al. *J. Heterocyclic Chem.* **47**, 363--367, 2010.
[262] Wang, G.-W., et al. *Bull. Chem. Soc. Jpn.* **79**, 454--459, 2006.
[263] Shi, D.-Q., et al. *Synth. Commun.* **39**, 664--675, 2009.
[264] Zare, L., & Nikpassand, M. *Chin. Chem. Lett*. **22**, 531--534, 2011.
[265] Fekri, L.Z., & Nikpassand, M. *J. Chil. Chem. Soc.* **57**, 1415--1421, 2012.
[266] Javid, A., et al. *Synth. React. Inorg. M.* **42**, 14--17, 2012.
[267] Banothu, J., et al. *J. Chem.* **2013**, 1--6, 2013.
[268] Hong, M., & Xiao, G. *J. Fluorine Chem.* **144**, 7--9, 2012.
[269] Heydari, A., et al. *J. Fluorine Chem.* **130**, 609--614, 2009.
[270] Wang, X.-S., et al. *Synthesis* **2006,** 4187--4199, 2006.
[271] Fan, X., et al. *Heteroatom Chem.* **18,** 786--790, 2007.
[272] Shi, D.-Q., et al. *J. Heterocyclic Chem.* **45**, 653--660, 2008.
[273] Rajanarendar, E., et al. *Indian J. Chem.* **50B,** 245--252, 2011.
[274] Vahdat, S.M., & Akbari, M. *Orient. J. Chem.* **27,** 1573--1580, 2011.
[275] Vahdat, S.M., et al. *Arabian J. Chem.*, In press.
[276] Dabiri, M., et al. *Catal. Commun.* **9**, 939--942, 2008.
[277] Moghadam, K.R., & Azimi, S.C. *J. Mol. Catal. A: Chem*. **363-364**, 465--469, 2012.
[278] Patil, D., et al. *Catal. Lett.* **144,** 949--958, 2014.
[279] Alinezhad, H., et al. *J. Chem. Sci.* **125,** 1517--1522, 2013.
[280] Makhey, D., et al. *Bioorg. Med. Chem.* **8,** 1171--1182, 2000.
[281] Li, D., et al. *Bioorg. Med. Chem.* **11,** 521--528, 2003.
[282] Martínez, R., et al. *Il Farmaco,* **55,** 631--636, 2000.
[283] Lielbriedis, I., et al. *Latv. PSR Zinat. Akad. Vestis. Kim. Ser. (Russ)* **1,** 39--41, 1971.
[284] Cortés, E., et al. *J. Heterocycle. Chem.* **25,** 895--899, 1988.
[285] Martínez, R., et al. *J. Heterocycle. Chem.* **27,** 363--366, 1990.
[286] Wang, X.-S., et al. *Tetrahedron Lett.* **46**, 7169--7173, 2005.
[287] Wang, X.-S., et al. *Arkivoc* **2006,** 117--123, 2006.
[288] Wang, X.-S., et al. *J. Heterocycl. Chem.* **43**, 989--995, 2006.
[289] Tu, S., et al. *J. Heterocycl. Chem.* **43**, 1621--1627, 2006.
[290] Kadutski, A.P., et al. *Russ. J Org. Chem.* **42**, 1383-1387, 2006.
[291] Nadaraj, V., et al. *Eur. J. Med. Chem.* **44,** 976--980, 2009.
[292] Wan, Y., et al. *Tetrahedron* **69**, 3947--3950, 2013.

[293] Dutta, B., et al. *Tetrahedron Lett.* **44,** 8641--8643, 2003.
[294] Osyanin, V.A., et al. *Chem. Heterocycl. Compd.* **50,** 1199--1202, 2014.
[295] Osipov, D.V., et al. *Russ. J. Org. Chem.* **49,** 398--402, 2013.
[296] Littman, J.B., & Brode, W.R. *J. Am. Chem. Soc.* **52,** 1655--1659, 1930.
[297] Snyder, H.R., & Brewster, J.H. *J. Am. Chem. Soc.* **70,** 4230--4232, 1948.
[298] Sirkecioglu, O., et al. *J. Chem. Res. Synop.* 502--506, 1995.
[299] Sarma, R.J., & Baruah, J.B. *Dyes Pigm.* **64**, 91--92, 2005.
[300] Khoramabadi-zad, A., et al. *J. Kor. Chem. Soc.* **46**, 541--544, 2002.
[301] Wu, L.Q., et al. *J. Braz. Chem. Soc.* **221,** 941--945, 2010.
[302] Rajitha, B., et al. *Tetrahedron Lett*. **46**, 8691--8693, 2005
[303] Pasha, M.A., & Jayashankara, V.P. *Bioorg. Med. Chem. Lett.* **17**, 621--623, 2007.
[304] Khosropour, A.R., et al. *Synlett* **2005**, 955--958, 2005.
[305] Patil, S.B., et al. *Synth. Commun.* **36**, 2163--2168, 2006.
[306] Kumari, P., et al. *Synth. Commun.* **38**, 637--648, 2008.
[307] Dabiri, M., et al. *Bioorg. Med. Chem. Lett.* **18,** 436--438, 2008.
[308] Kumar, P.S., et al. *Arkivoc* **2006,** 46--50, 2006.
[309] Zarei, A., et al. *Dyes Pigm.* **85**, 133--138, 2010.
[310] Puri, S., et al. *Heterocycl. Lett.* **1**, 269--274, 2011.
[311] Kantevari, S., et al. *Catal. Commun.* **9**, 1575--1578, 2008.
[312] Wu, H., et al. *Synth. Commun.* **39,** 3762--3771, 2009.
[313] Gong, K., et al. *Dyes Pigments* **80**, 30--33, 2009.
[314] Fang, D., & Liub, Z.-L. *J. Heterocycl. Chem.* **47,** 509--512, 2010.
[315] Rahmati, A. *Chin. Chem. Lett.* **21**, 761--764, 2010.
[316] Heravi, M.M., et al. *Synth. React. Inorg. M.* **41**, 616--620, 2011.
[317] Khazdooz, L., et al. *Iran. J. Catal.* **1,** 1--10, 2011.
[318] Zare, A., et al. *J. Mol. Liq.* **167**, 69--77, 2012.
[319] Zolfigol, M.A., et al. *C.R. Chim.* **15**, 719--736, 2012.
[320] Zhou, Z., et al. *Iran. J. Catal.* **3,** 237--242, 2013.
[321] Naeimi, H., & Nazifi, Z.S. *J. Chin. Chem. Soc.* **60,** 1113--1117, 2013.
[322] Naeimi, H., & Nazifi, Z.S. *C. R. Chim.* **17**, 41--48, 2014.
[323] Moosavi-Zare, A.R., et al. *Chin. J. Catal.* **35**, 573--578, 2014.
[324] Shirini, F., et al. *Chin. Chem. Lett.* **25**, 341--347, 2014.
[325] Kundu, D., et al. *Green Chem. Lett. Rev*. **4,** 205--209, 2011.
[326] Masoumeh, Z., et al. *Chin. J. Chem.* **29,** 1441--1445. 2011.
[327] Janardhan, B., et al. *J. Chem. Pharm. Res.* **4,** 519--525, 2012.

[328] Zang, H., et al. *Chin. J. Chem.* **30**, 362--366, 2012.
[329] Zare, A., et al. *Iran J. Catal.* **2,** 107--114, 2012.
[330] Iniyavan, P., et al. *Res. Chem. Intermed.* **41,** 7413--7426, 2015.
[331] Cardellicchio, C., et al. *Tetrahedron: Asymmetry* **21**, 507--517, 2010.
[332] Betti, M., & Foa, V. *J. Chem. Soc.* **84**, 511--517, 1903.
[333] Ahmed, N., et al. *J. Am. Chem. Soc.* **66**, 2403--2405, 1934.
[334] Burke, W.J., et al. *J. Am. Chem. Soc.* **76,** 1677--1679, 1954.
[335] Smith, H.E., & Cooper, N.E. *J. Org. Chem.* **35,** 2212--2215, 1970.
[336] Hanumanthu, P., & Ratnam, C.V. *Indian J. Chem.* **15B,** 1019--1021, 1977.
[337] Reddy, V.P., et al. *Indian J. Chem.* **21B,** 148--149, 1982.
[338] Cimarelli, C., et al. *J. Org. Chem.* **66,** 4759--4765, 2001.
[339] Lu, J., et al. *Tetrahedron Lett.* **43,** 8367--8369, 2002.
[340] Szatma´ri, I., et al. *Tetrahedron* **59**, 2877--2884, 2003.
[341] Szatma´ri, I., et al. *J. Org. Chem.* **69,** 3645--3653, 2004.
[342] Dong, Y., et al. *J. Org. Chem.* **70,** 8617--8620, 2005.
[343] Agag, T. *J. Appl. Polym. Sci.* **100,** 3769--3777, 2006.
[344] Turgut, Z., et al. *Molecules* **12,** 345--352, 2007.
[345] Zheltukhin, V.F., et al. *Mendeleev Commun.* **17,** 239--240, 2007.
[346] Li, Y.H., et al. *Acta Cryst*. **E64,** o1972, 2008.
[347] Zhang, Y., & Li, Y.H. *Acta Cryst.* **E65,** o1796, 2009.
[348] Sapkal, S.B., et al. *Green Chem. Lett. Rev.* **2,** 57--60, 2009.
[349] Liu, B., et al. *Synthesis* **2009,** 3227--3232, 2009.
[350] Sadaphal, S.A., et al. *Green Chem. Lett. Rev.* **3,** 213--216, 2010.
[351] Kategaonkar, A.H., et al. *Org. Commun.* **3,** 1--7, 2010.
[352] Mathewa. B.P., et al. *Euro. J. Med. Chem.* **45**, 1502--1507, 2010.
[353] Srimannarayana, M., et al. *Synthetic Communications*, **44,** 3450--3455, 2014.
[354] Dhakane, V.D., et al. *C. R. Chim.* **17**, 431--436, 2014.
[355] Mahato, S., et al. *Chem. Commun,* **50,** 332--334, 2014.