I.A. Introduction

C-H bond activation is a series of mechanistic processes by which stable carbon-hydrogen bonds in organic compounds are cleaved.[1] The purpose is to enable functionalization of these molecules, leading to the synthesis of more complex intermediate or product compounds often containing C-O, C-C and C-N bonds.[2] The ability to cleave the C-H bond enables inexpensive feedstock molecules to be transformed into commercially valuable molecules.[3]

Figure I.1: C-H Functionalization

Directed C-H activation enables selectivity and specificity in the synthesis of more complex molecules of importance in pharmaceutical and fine chemical applications.[4]

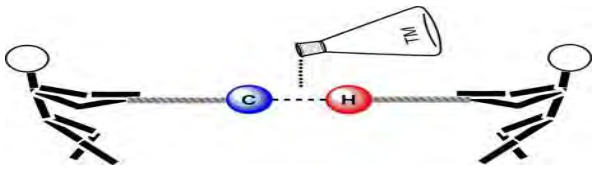


Figure I.2: C-H Activation

C−H activation has long pledged a means to decrease step-count and hence mass intensity of chemical developments.[5]There are a numbers of mechanisms by which C-H bonds are activated via oxidative addition, σ-Bond metathesis, electrophilic substitution, etc. By definition, C-H activation occurs through catalytic mechanisms. As an example, C-H activation occurs when transition metals such as Pt, Rh, Ir, etc. are used in catalytic oxidative addition reactions.

In a broad sense, the term "CH functionalization" (synonyms include CH- activation, bond activation and transformation) can be defined as the conversion of carbon–hydrogen bonds into carbon–carbon or carbon–heteroatom bonds [6]. The interest of C-H functionalization is increasing day by day and more than 500 publications is achived till 2011 [6]. (Figure **I.A.3,** See figure below in bar chart). Over the past two decades there has been an explosive growth in the development of methods for C–H functionalization and the application of these technologies for the synthesis of complex targets such as natural products and pharmaceutical agents.

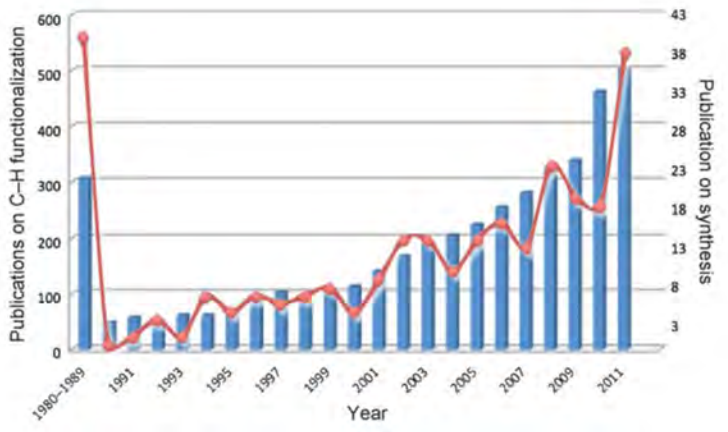


Figure I.3: No of Publication year wise

In leu of enormous contributions and interest of many researchers in this field, where the unreactive C–H bond can now become as key synthon for both C–C and C–X (X = O, S, Se, N, Cl, Br, I etc.) in various moieties.

Science dealing with heteroaromatic moieties are very much important and plays a vital role in pharmacological aspect.[7]

Over the past decade, atom- and step-economical C–H functionalization strategies have attracted the attention of many research groups in both academic and industrial sectors.[8] reflecting the ubiquity of heteroarenes, strategies that enable late stage modification of these molecules by directed functionalization of their C–H bonds have now become highly desirable[8].Due to high interest in this field chemists have turn out to be more mindful for

Conservation of natural resources and protection of the environment through the sensible route selection for making complex natural products.

As because of ubiquitous nature of C–Het (F, O, S, N, and P) as well as C–C bonds in organic compounds, modern synthetic strategies are based on the activation of these chemical bonds for the C–H functionalization. Hence the formation of heteroarenes have now become highly desirable. Although substantial evolution has been achieved in this area, a systematic review on the C–H functionalization of heteroarenes with these alternative coupling partners also had conducted in 2021.[9]

Glorious and et al[8] reported the research areas and looking for to overcome the sustainable challenges of C–H activation to minimize the use of abundant metal catalysts, avoidance of static directing groups, metal oxidants, and replacement with bioderived solvents

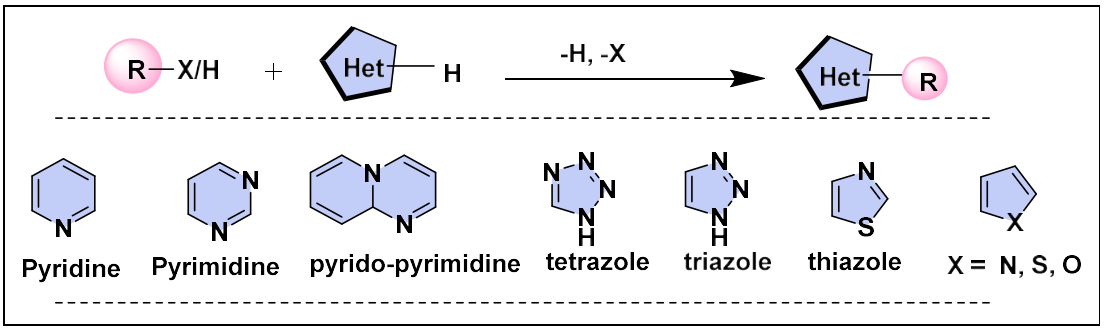


Figure I.4:

C–H functionalization of heteroarenes and the major heteroarylframes in small molecule drugs

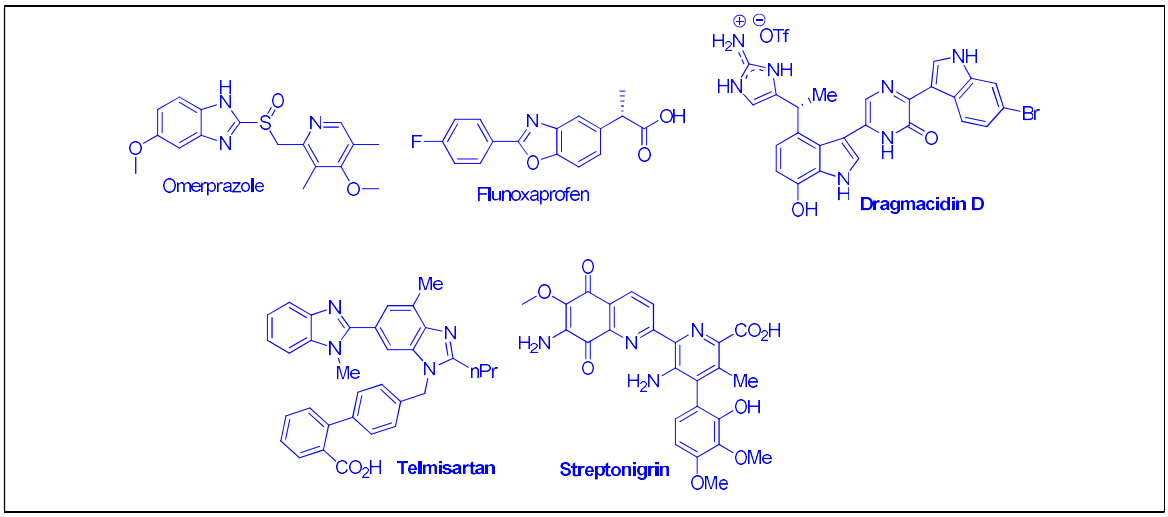


Figure I.5: Biologically active heterocycles

I.A.1: Reason of choosing 4-Pyrimidone as my research work:

Pyrimidines (**1**) are highly significant heterocycles in biology and are by far the most common members of the diazine family. Both cytosine (**6**) and uracil (**8**) are found in Figure 2(b), and both are components of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA).The said backbone do have their immense dominancy in many natural products such as vitamin B1 (thiamine) and many other synthetic compounds, such as barbituric acid (9) and Veranal (10) which are used as hypnotics [31] (**Figure 2b**).

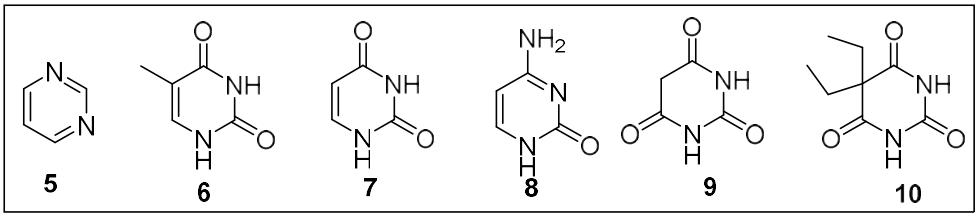


Figure I.6: Some exciting component in RNA, DNA

The comprehensive literature study reveals that the compound containing pyrimidone exhibited wide range of pharmacological activities, surrounding pyrimidines nucleus. Along with that various analogues of pyrimidines have been found to possess, antiallerggic [11], antiviral [12],[14], antifungal [15-18], antileishmanial [19], antihypertensive [20, 21], antibacterial [22-29], antiallerggic [30],antioxidant [31, 32], analgesic [33], antihistaminic [34], antidiabetic [35]. herbicidal[36], anticonvulsant [37], antipyretic [38], anti-inflammatory [39, 40] and anticancer activities [41-44] and several pyrimidines analogues has been found to exhibit potential depressant properties [45, 46].

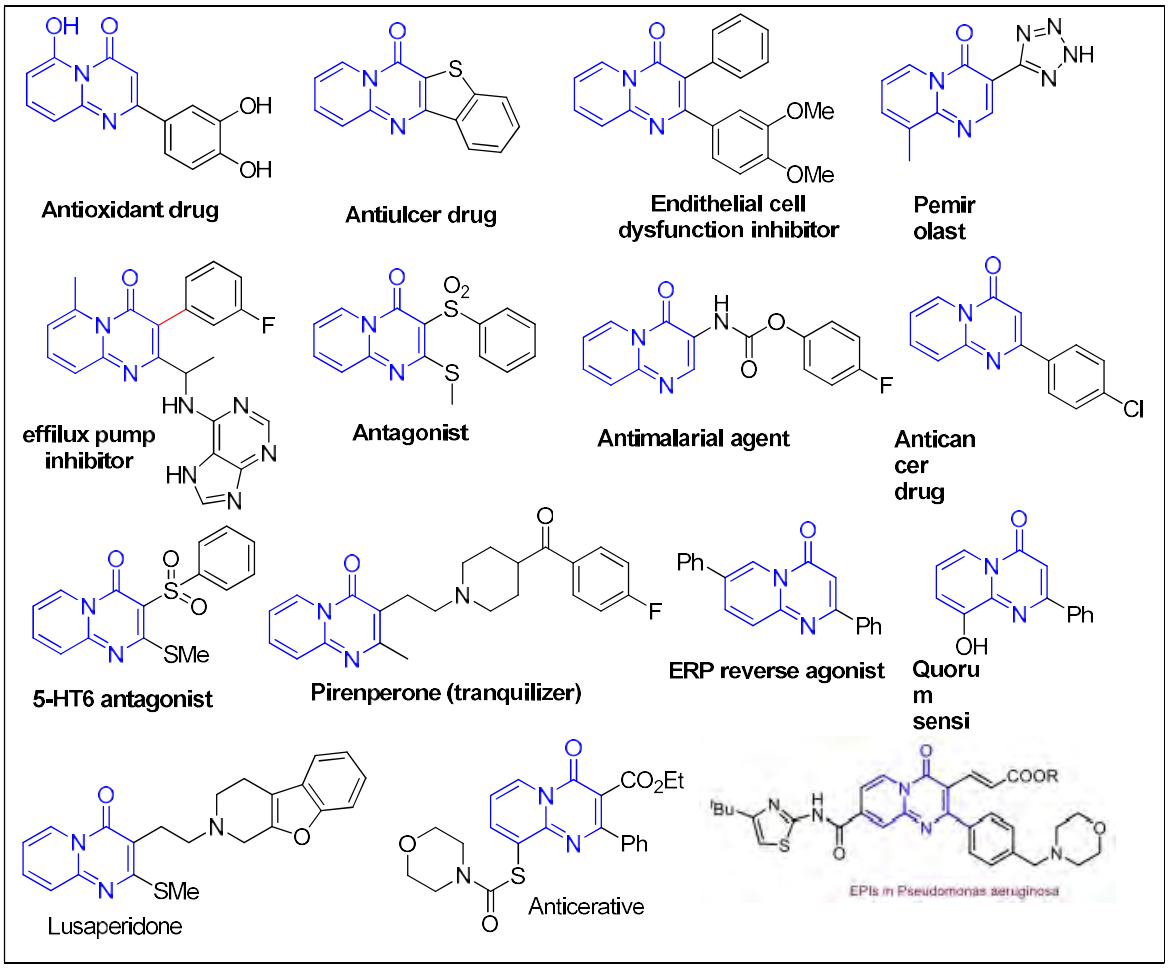


Figure I.7: List of some marketed drug having 4-Pyrimidone backbone

After going through some of the current available literature[47]it is clear enough that more or less 70% of highest selling commercial drugs are having at least one hererocylic aromatic entity [1], especially in the form of aryl and biaryl heterocyclic aromatic compounds [47]. Numerous medical uses have been discovered for 4 pyrimidone and its congeners (**Figure I.A.5**). It has been reported that several 4H-pyrido[1,2-a]pyrimidin-4-one compounds (Figure 1) inhibit the efflux pump activity of pseudomonas aeruginosa, pirenperone treats for common tranquilizer agent, paliperidone as an antipsychotic drug, pemirolast as an antiasthmatic drug, while lusaperidone is an antidepressant drugs[48, 49]etc. M. J. Angove and F. Huang describes[48] the traditional and modern attitudes to explore the synthesis of 2-aryl- and 2-alkyl-4H-pyrimidin-4-ones scaffold. There are number of approaches a-vailable for the C-H functionalization of 4 pyrimidones like direct transition metal catalysed, directed metal catalysed as well as transition metal-free methods are being discussed below.

I.B: Importance and challenges of C-H functionalization:

I.B.1: Importances:

Reinforcing Synthesis:C-H functionalization of 4-pyrimidone enact for widely diverse transformation of inactive C-H bond into various C-X (X=SCN, SeCN, NO_2, CF_3, CHO etc) bioactive molecules from prefunctionalized starting moieties. This synthetic approaches makes more reliable, convient and environment friendly.

Efficiency and Selectivity: C-H functionalization procedures rovides high level of regioselective and chemoselective enable product. This selective modification of particular C-H bond of a complex organic molecule over others.

Atom Economy: By means of C-H functionalization we could decrese number of steps and which enhances the atom economy of the methodology and minimizing the waste production. This is complies the principal of Green Chemistry.

Diversity in Drug Discovery: N- based substances; pyrimidone in particular, is extensively utilized in practically all parmaceutical sectors. Certain functional groups can be added to these molecules through C-H functionalization.

Financial Aspects: By eliminating the need for costly and frequently hazardous chemicals, direct C-H functionalization increases the overall synthesis's viability from an economic standpoint.

I.B.2: Challenges:

Site Selectivity: It can be difficult to achieve strong site selectivity in a complicated molecule with several C-H bonds. Research is still being done to create techniques that can specifically target a particular C-H bond.

Catalyst Development: A crucial component is the creation of effective and specific catalysts for C-H activation. Catalysts must be strong, economical, and able to activate particular C-H bonds in moderate circumstances.

Functional Group Compatibility: The presence of specific functional groups in the molecule affects a number of C-H functionalization events. Creating reactions that work with a wide variety of functional groups is a difficult task.

Intramolecular vs. Intermolecular Reactivity: it can be difficult to distinguish between intramolecular and intermolecular reactions and to regulate the selectivity between them, particularly in complex substrates.

Scaling up reactions: Although a lot of C-H functionalization techniques are effective in small-scale reactions however it is still difficult to transfer these reactions into efficient, high-yield industrial processes.

I.C: Classification of C-H functionalization

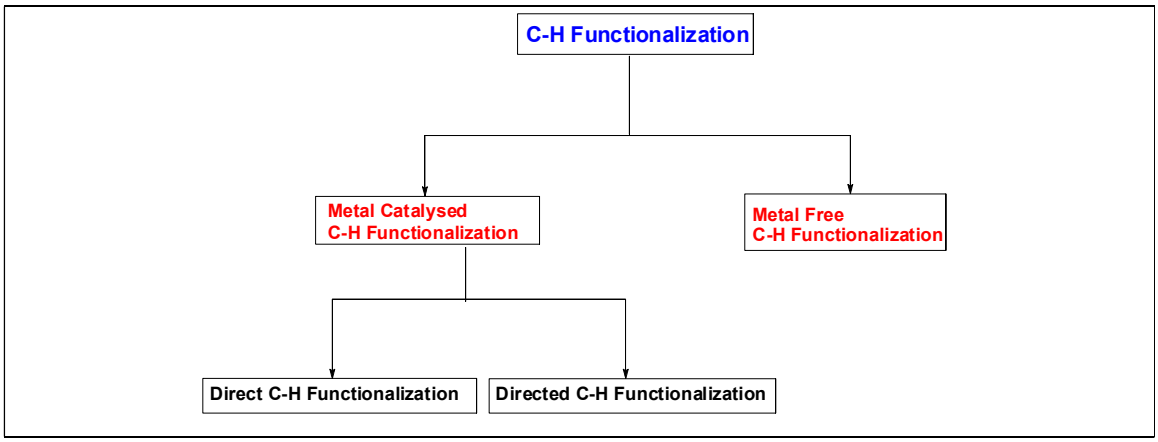


Figure I.8: Classification of C-H functionalization

I. C.1: Metal Catalysed C-H functionalization:

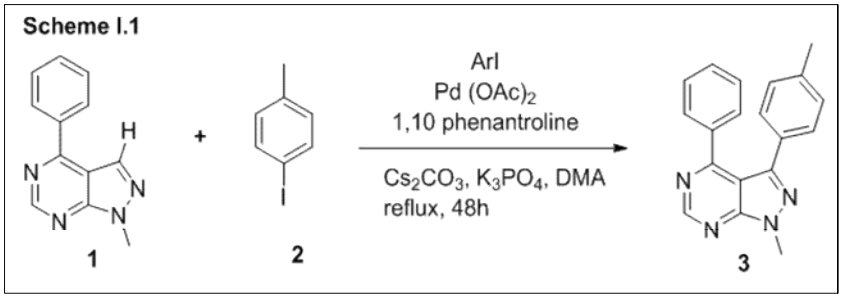
I.C.1.1: Direct C-H functionalization

In 1967 the first report on direct C–H functionalization using palladium chloride in AcOH was reported by Moritani and Fujiwara[50]. In order to break a bond, the traditional synthetic

-protocol requires high bond dissociation energies. The subsequent insertion step also requires more harsh conditions, which are less compatible with different functional groups. One of the most important factors contributing to the broad applicability of C-H activation methods is the control of their site selectivity, particularly since the majority of compounds contain a variety of C-H bond and functional group types.

Murai and Chatani's group[51,52]strategy direction has proven to be the most effective methods. This field of synthetic organic chemistry has grown incredibly effective since their groundbreaking work in the late 1990's, producing a wide range of solutions with a broad range of applications in materials science and the pharmaceutical industry.

Guillaumet[53] in 2017 (Research on nitrogen containing bicyclic compounds seems to go on forever in the fields of Biorganic chemistry. In this work they have reported a three-step, efficient method from allopurinol to the pyrazolo[3,4-d]pyrimidine scaffold. The first instance of regioselective C-H arylation catalyzed by palladium involved this crucial intermediate, which allowed access to a library of 3-substituted-1-methyl-4-phenyl-1H-pyrazolo[3,4-d]pyrimidines (Scheme-**I.1)**.



Scheme I.1: Strategy for the synthesis of C-3 arylated pyrazolo[3,4-*d*]pyrimidines

Mechanism:

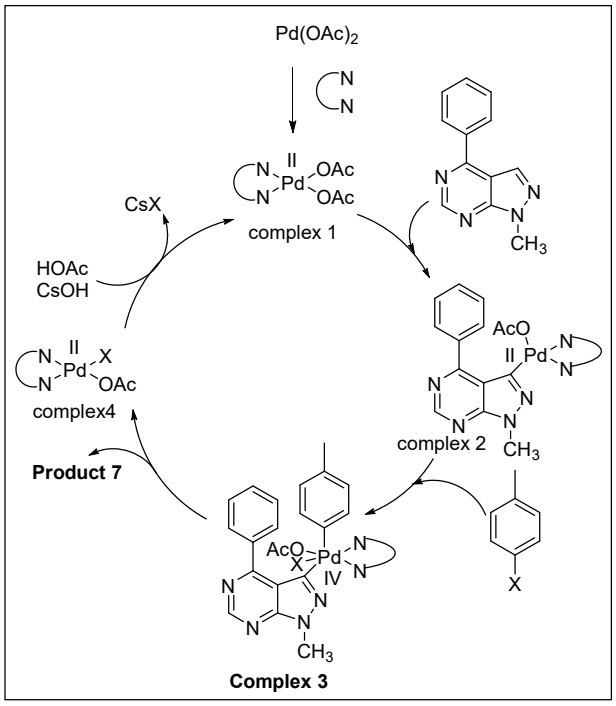
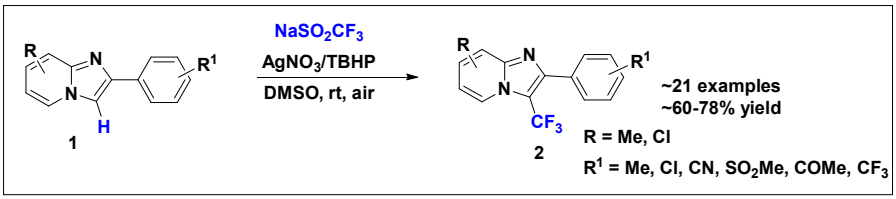


Figure I.9: Mechanistic outline of Scheme I.1

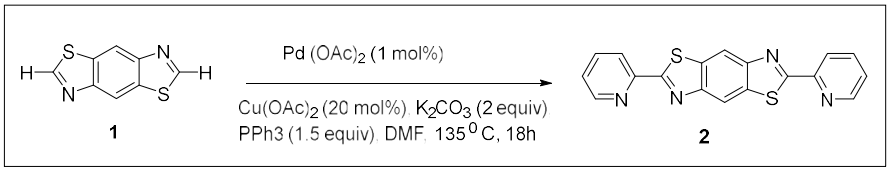
In 2015, Hajra et al. firstly reported a direct and straight forward method for the regioselective trifluoromethylation of imidazopyridines through sp2 C−H functionalization using Langlois reagent in ambient temperature in open air (Scheme-**I.2)**.[54] Wide range of 3-(trifluoromethyl)imidazo[1,2-a]pyridine derivatives with broad functionalities were synthesized employing catalytic amount of $AgNO_3$/TBHP at room temperature. This protocol was further applied to imidazo heterocycles like imidazo[2,1-b]thiazole and benzo[d]imidazo-[2,1-b]thiazole



Scheme-I.2: Regioselective trifluoromethylation of imidazopyridine

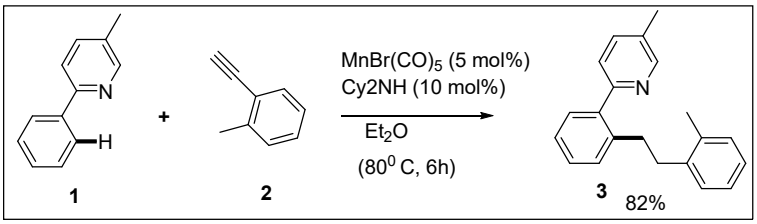
Simon B. Blakey et al demonstrated a single pot methodology to excel densely functionalized benzobisthiazole moieties**.** Palladium and copper were used as cocatalysts in this C–H bond

functionalization on the benzobisthiazole system.[55]Because the products are electron-poor, the effectiveness of this methodology has an impact on the materials and organic electronic-communities, which resulted valuable development of light-emitting diodes and organic photovoltaic cells



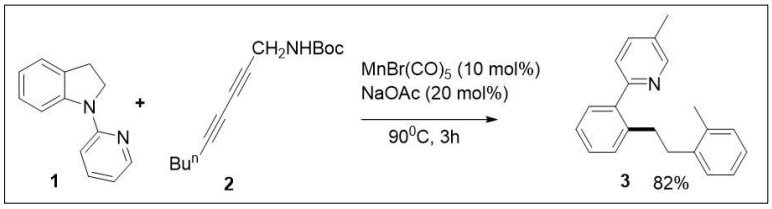
Scheme I.3: Palladium catalyzed bis-arylation of benzo dithiazole derivatives

Research on Mn-catalyzed[56] of high regio and chemo selective synthesis was initiated by Wang and et al and achieved anti-Markovnikov *E*-configured olefins with excellent yields using the simple $MnBr(CO)_5$ catalyst (**Scheme I.4)**



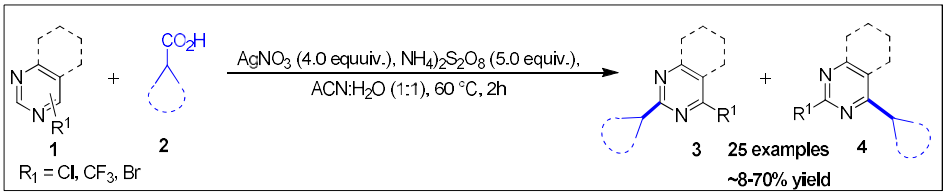
Scheme I.4: Mn-Catalyzed Aromatic C−H Alkenylation

Later Glorius and co-workers[57]reported a selective synthesis of compound **3** in high yield from 1,3-enynes and pyrroles using $MnBr(CO)_5$ as a catalyst (**Scheme: I.5)**. Whereas the reaction became inactivein the presence of Rh- and Ru-based catalysts.



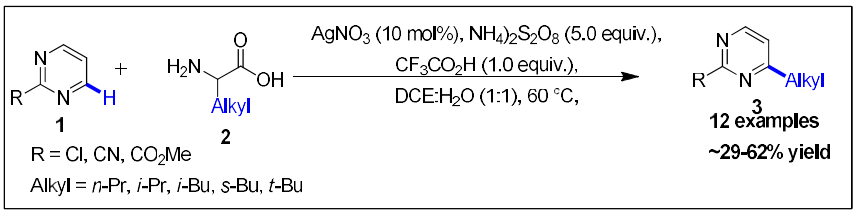
Scheme I.5: Co-Catalyzed Aromatic C−H functionalization

In 2015, Estrada et al reported a one-step protocol for regioselective C(sp^2)–H alkylation of substituted pyrimidine derivatives in the presence of an excess of $AgNO_3$ and $(NH_4)_2S_2O_8$. Combination of these oxidative reagents allowing the direct installation of alkyl group at either C-2 or C-5 position of substituted pyrimidines **1**.A variety of alkanoic and (hetero)cycloalkanecarboxylic acids (**2)** act as source of alkyl group in this reaction (Scheme I.6). [58]



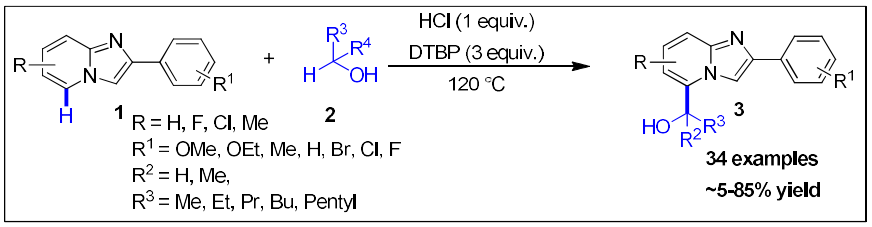
Scheme I.6: C-H Functionalization of pyrimidines with carboxylic acid of carbocycles and or heterocycles to access tri- and tetrasubstituted pyrimidines

Similarly, Baxter and Mai [59]in 2016 carried out the C–H alkylation of a variety of pyrimidines with unprotected amino acids. This is a general and effective technique that produces monoalkyl-substituted pyrimidines by forming stable alkyl radicals from amino acids under the classic Minisci conditions (silver catalyst and persulfate oxidant)



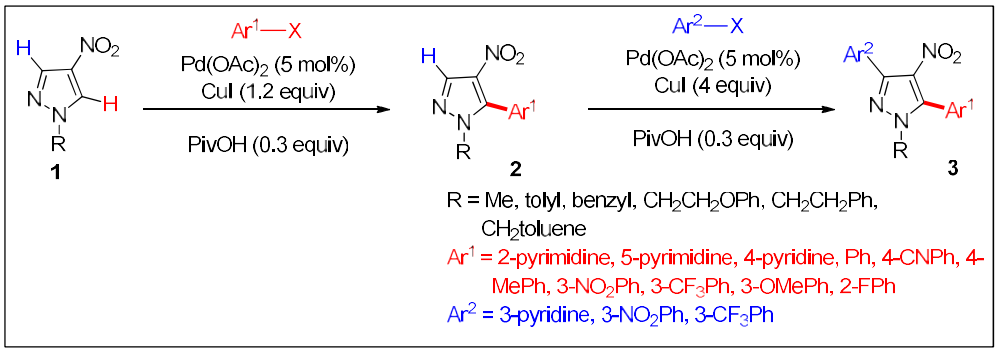
Scheme I.7: Direct C–H alkylation of 2-substituted pyrimidines with unprotected amino acids

A novel method for the synthesis of hydroxyalkylations of imidazo[1,2-a]pyridines **1** at the C-5 position was developed in 2019 by Yan and his associates. This reaction goes through a radical process using the DTBP reagent as a promotor (**Scheme I.C.8**)[60a].It was found that the technique of using non-metallic catalysis to activate the C(sp^3)–H bond was effective when applied to 2-phenylimidazo[1,2-a]pyridine, which has phenyl ring groups that can either donate or withdraw electrons.



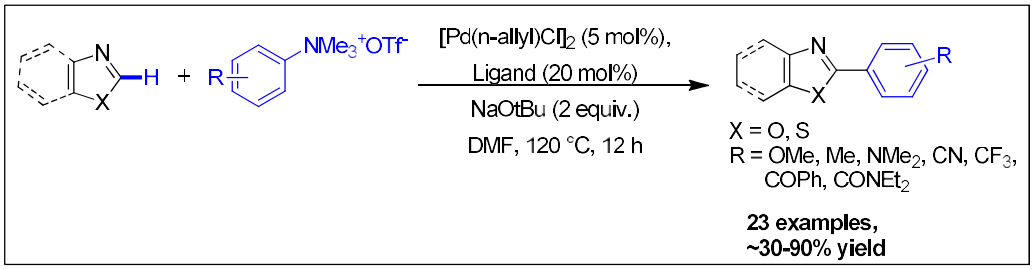
Scheme I.8: C-5 hydroxyalkylation of imidazo[1,2-*a*]pyridines with alcohols

Iaroshenko and Langer studied the transition-metal-catalyzed arylation reaction of 4-nitropyrazoles (**1**) with two different d-metals, i.e. Pd and Ni catalysed, using CuI as an additive. The reaction with Pd catalyst showed better yields over Ni catalyst (**Scheme: I.9)** [60b, 83]The reactions result C-5 arylated product with exclusive regioselectivity. Furthermore, they have extended this methodology to activate the C-3 of nitropyrazoles after arylation of C-5. Descibed approach was efficacious for the synthesis of pyrazoloisoquinolines derivatives.



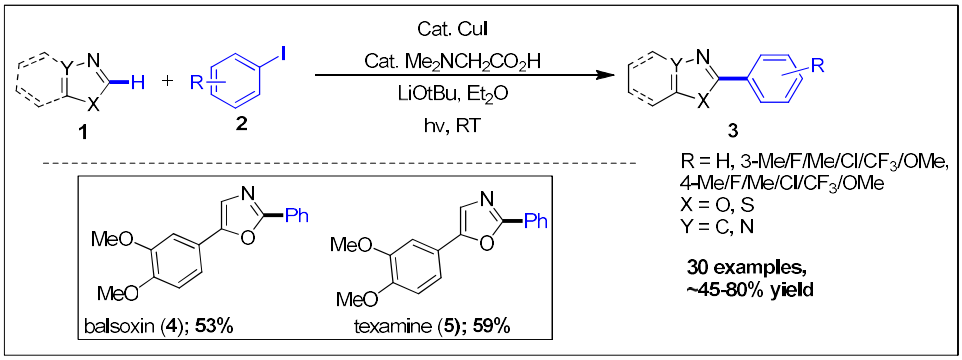
Scheme I.9. Regioselective and Guided sequencial C−H Activation of 4-Nitropyrazoles

For the first time 2015, Wang and his co-worker reported Pd-catalyzed C-H/C-N cleavage was used to C-H arylate (benzo)oxazoles or (benzo)thiazoles with aryltrimethylammonium triflates. Using activated and deactivated aryltrimethylammonium triflates, azoles, thiazoles, benzoxazoles, and benzothiazoles were arylated to yield 2-aryl(benzo)oxazoles or 2-aryl(benzo)thiazoles in good to excellent yields. (**Scheme I.10**).[60c, 84]



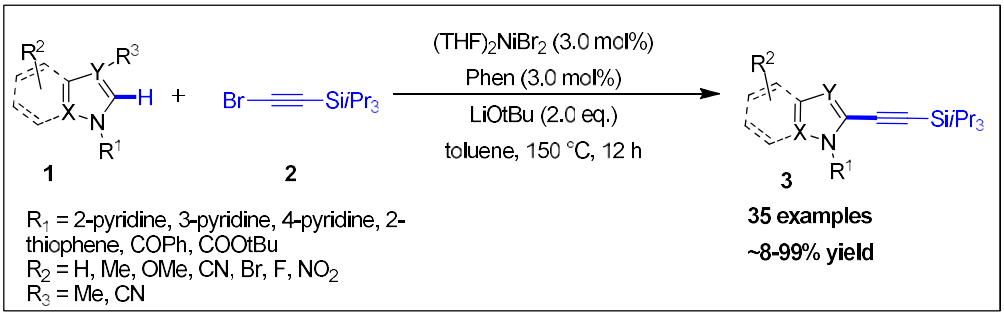
Scheme I.10: Palladium-Catalyzed C–H Arylation of (Benzo)oxazoles or (Benzo)thiazoles with Aryltrimethylammonium Triflates

Lutz Ackermann et al. in 2016 described the first photoinduced C-H arylation in heteroarenes using inexpensive copper catalysts (**Scheme I.11**).[60d, 85] This C-H functionalization with organic electrophiles accomplished direct arylations of several aromatic and non-aromatic heterocycles with generous scope. This methodology provided a step-economical access to balsoxin and texamine alkaloid (natural products).



Scheme I.11: Photoinduced copper-catalyzed C-H arylation and synthesis of alkaloids

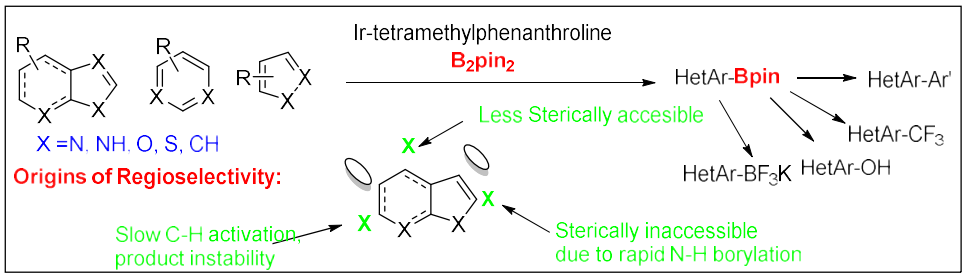
Group of Benudhar Punji in 2017 described a general nickel-catalyzed method for the alkynylation of heteroarenes through monodentate chelation (Scheme **I.12**). [60e, 86] Several heterocycles **1**, including pyrroles, indoles, imidazoles and pyrazole, efficiently coupled with (triisopropylsilyl)alkynyl bromide **2**, and synthetically important functional groups, such as ethers, halides, nitrile, nitro..



Scheme I.12: Ni-catalyzed C-H functionlization of heterocycles

Under metal catalysis, the C–H bonds in pyrroles, furans, and thiophenes were converted to significant functional groups, resulting in the formation of valuable organic compounds that might not be achievable through conventional synthetic methods. These single heteroatom-containing five-membered heterocycles make up the fundamental building blocks of many natural products and pharmaceutical compounds. Most recent advancements in this field have been made by different research groups using transition-metal catalysis. In recent decades, various strategies for pyrroles, furans, and thiophenes have evolved, including C-H arylation, alkenylation, alkynylation, alkylation, borylation, silylation, and amidation.

A very impressive study on the iridium-catalyzed C–H borylation of aromatic heterocycles was published in 2014 by Larsen and Hartwig, [60f, 87] (Scheme I.13).1.They showed how effective borylation is at functionalizing heteroarenes with iridium catalyst and consistent selectivities.



Scheme I.13: Iridium-catalyzed C−H borylation of aromatic heterocycles

I.C.1.2: Directed C-H functionalization

Among the reasons considering C-H activation methods having its broad utility, one of the most critical condition which leads to control of its site selectivity, especially as most compounds contain varities types of C-H bonds and functional groups.Directing group strategy has been the most successful approach, pioneered by Murai and Chatani.[61,62] Since their seminal work in the late 1990s, this area of synthetic organic chemistry has become extremely effective, leading to a wide variety of solutions with broad range of application in materials science and the pharmaceutical industry.

(1) The creation of novel directing groups that can be easily eliminated or transformed into functional elements

(2) Broadening the scope from the more traditional functionalization of sp2 C-H bonds to sp3 C-H bonds.[72,73]

(3)The methodology's application in order to introduce a wider range of functionality

(4) Modification of the directing influence away from just Ortho- functionalization.[71-77]

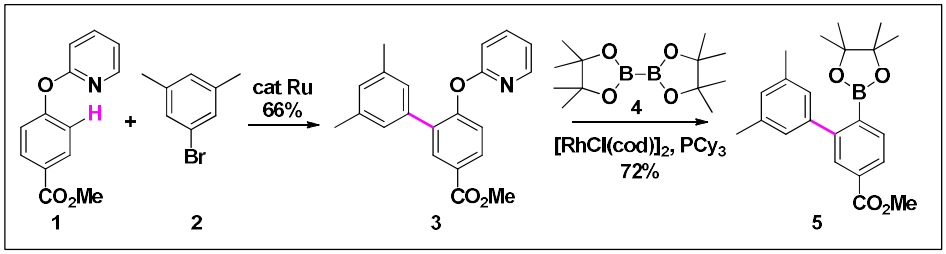
(5) Improvement of the catalytic efficiency to the point where very little precious metal or earth-abundant catalyst is required.[69,77]

Briefly describing some of the recent innovative advances was performed in directed C−H functionalization and highlighting as given below.

Recently, a reasonable amount of chemistry work has been done to understand how a modification to the nature of the directing group influences the effectiveness of the overall chemistry. Yu group presented substantial progress in using weakly coordinating directing groups which enable the global catalytic cycle to proceed more effectively and includes groups that are more synthetically handy in successive transformations.[78,79]

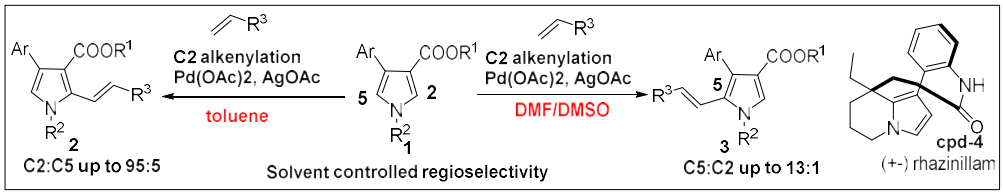
An additional noteworthy progression would be the creation of guiding groups with easy removal. This has prompted important efforts to create "traceless" directing groups.[80] Tobisu and Chatani describe how they overcame this difficulty by first performing a one-pot, catalytic borylative cleavage of the directing group, which installed the adaptable boryl functional group, and then employing an aryl 2-pyridyl ether, an incredibly efficient directing group, to perform a selective directed C-H functionalization.[81]

This method can be demonstrated by the ruthenium-catalyzed arylation of the aryl 2-pyridyl ether **(1)** with the bromoaryl (**2**), which results in the arylated product **(3)**. Next, the directing group (**Scheme: I.14**) is replaced by a rhodium-catalyzed borylation with bis(pinacolato)diboron (**4**), which results in the boryl derivative (**5**).



Scheme I.14: Rh-Catalyzed Aromatic C−H functionalization

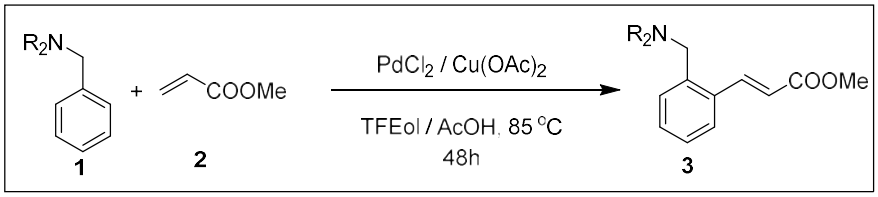
One of the main challenges in the C-H functionalization of heterocycles is creating reaction conditions and/or reagents that allow for flexible control of site selectivity. In the palladium-catalyzed C−H alkenylation of 4-aryl-1*H*-pyrrole-3-carboxylate (**Scheme: I.15**) Lin, Yao, and colleagues show that C-2 alkenylation to form **2** occurs in toluene (eq 14), whereas C-4 alkenylation to form **3** occurs in DMF/DMSO.[82a] When a polar aprotic solvent isn't present, the ester group binds to the catalyst and guides the reaction toward C-2. However, in a polar solvent, the reaction takes place at a location that is more vulnerable to electrophilic attack by nature.



Scheme I.15: Solvent-Controlled Switchable C–H Alkenylation of 4-Aryl-1*H*-pyrrole-3-carboxylates

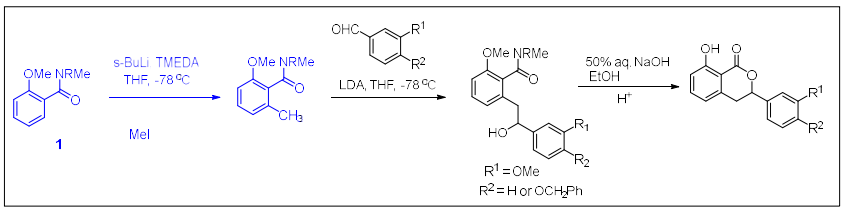
Extensive research has been conducted on the directed C–H functionalization of benzene derivatives with amino groups, aimed at enhancing the functionalization of the benzene moiety through the use of stoichiometric amounts of metal complexes. In subsequent stages, catalytic amounts of metal complexes have been employed for an extended period.

Palladium, with its distinctive properties, has prominently emerged as a leading catalyst in this context. Shi and collaborators [82b] achieved successful palladium-catalyzed ortho C–H olefination directed by an N,N-dimethylaminomethyl group.



Scheme I.16: Iridium-catalyzed C−H borylation of aromatic heterocycles

Watanabe and Snieckus[82c] have utilized a useful strategy for synthesis of dihydroisocoumarin natural products following the directed metalation of tertiary benzamide (**Scheme I.17)**



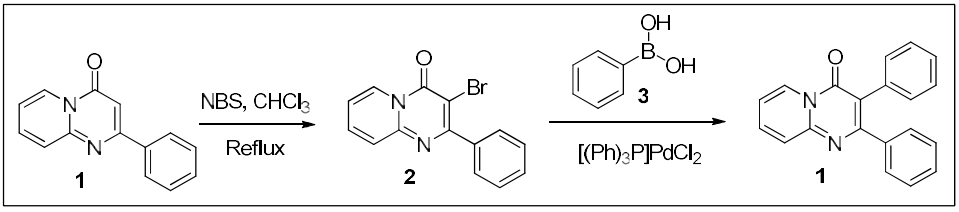
Scheme I.17: Directed C-H activation to prepare dihydroisocoumarin natural product

I.C.2: Metal Free C-H functionalization:

The process of changing carbon-hydrogen (C-H) bonds in organic compounds without the use of metal catalysts is known as "metal-free C-H functionalization." Traditional organic synthesis often relies on transition metal catalysts to facilitate the activation of C-H bonds, enabling the formation of new chemical bonds. However, metal-free C-H functionalization seeks to achieve similar transformations without the need for transition metals.

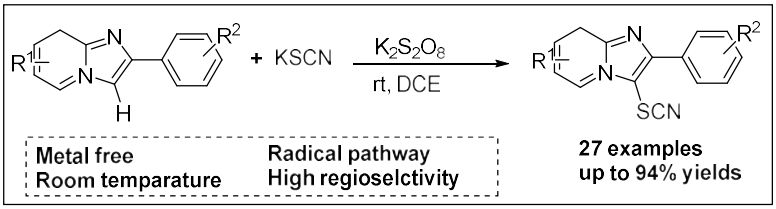
The concept of metal-free C-H functionalization has been explored for quite some time, and it is challenging to pinpoint the absolute first report. However, the development of metal-free C-H functionalization methods has gained significant attention in recent decades. One early example is the work by Professor E.J. Corey in the late 1970's, which explored metal-free oxidative coupling reactions involving C-H activation.

In 2013, Motta et al. used N-bromosuccinimide in chloroform under reflux conditions to bromate derivatives (1) of 4H-pyrido[1,2-a]-pyrimidin-4-ones. Through this procedure, 3-bromo-4H-pyrido[1,2-a]-pyrimidin-4-ones (**2**) were formed (**Scheme I.18**) [88]. Subsequently, a Suzuki coupling reaction was carried out on the bromo intermediate with aryl boronic acids (**3**) employing bis(triphenyl phosphine)palladium(II) dichloride in EtOH/toluene, leading to the synthesis of 3.



Scheme I.18: NBS-promoted bromination and subsequent Suzuki coupling of 4 Pyrimidone

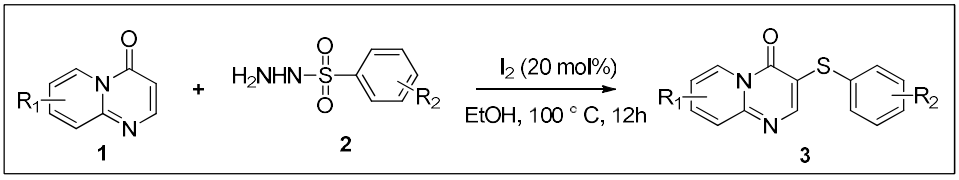
In 2015 Wang et al reported[89]straightforward and easy way to thiocyanate imidazoheterocycles with good regioselectivity at room temperature via sp2 C-H functionalization has been discovered.



Scheme I.19: Catalyst-Free Regioselective C-3 Thiocyanation of Imidazopyridines

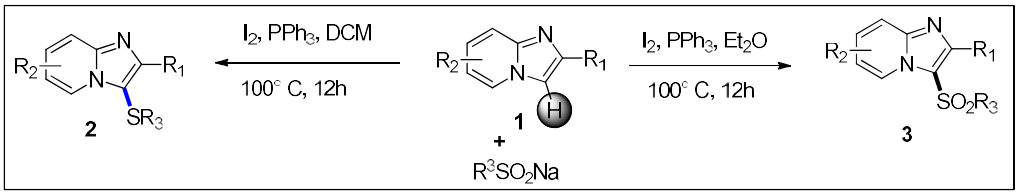
A variety of C-3 thiocyanated imidazopyridines are produced in a moderate to good yield. A variety of imidazopyridine derivatives with intriguing pharmacological properties can be accessed with mild and selective ease using the present method.

In 2018, Wang et al. reported iodine catalyzed regioselective C3 sulfenylation of 4H-Pyrido-[1,2-a]pyrimidin 4-ones 1 with sulfonyl hydrazides 2, by heating 100^0C for 12 h in ethanol (**Scheme I.20**) [90]. Various substituted 4*H*-pyrido[1,2-a]pyrimidin-4-one such methyl and halogen gave afforded sulfonated product in 71–80% yields.



Scheme I.20: Iodine catalysed metal free regioselective C3 sulfenylation of 4Hpyrido-[1,2-a]pyrimidin-4-ones

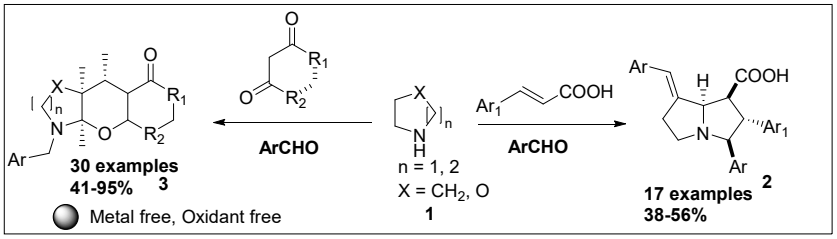
Drawing inspiration from enzymatic aerobic oxidation processes, Song and colleagues in 2018 [93]effectively accomplished the iodine-mediated sulfonylation and sulfenylation of C3-imidazo[1,2-a]pyridines using sodium sulphonate in 2018 (**Scheme I.21**) [91]. The presence of iodine and sodium carbonate led to the formation of sulfonylated products 6, while iodine and triphenylphosphine facilitated the generation of sulfenylated products



Scheme I.21: I_2-promoted sulfonylation and sulfenylation of C3-imidazo[1,2-*a*]pyridines with sodium sulfonates

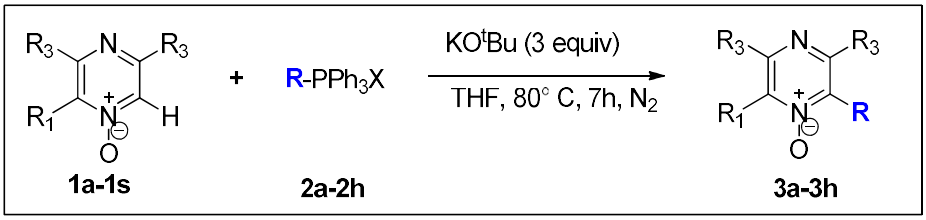
In the year 2018 a new multicomponent reaction,[92] facilitated by C–H functionalization, has been introduced. This innovative process involves N-heterocycles, dinucleophile, and dipolarophile. It successfully accomplishes direct α- and more challenging β-C(sp3)–H functionalization of aliphatic N-heterocycles (**Scheme I.22)** eliminating the need for metallic reagents and oxidants. This achievement holds true under both conventional and microwave-assisted heating conditions. In a single step, the reaction forms up to five carbon–carbon and

carbon–heteroatom bonds in a highly diastereoselective manner, providing a rapid route to intricate heteropolycycles



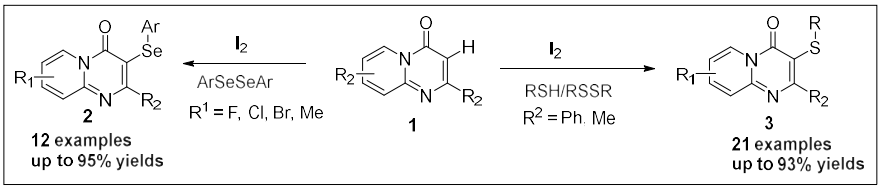
Scheme I.22: Direct α and β-C(sp3)–H functionalization of aliphatic N-heterocycles without the use of metalreagents and oxidants

In 2019 the synthesis of diazine derivatives that are alkylated holds significance for their practical application in pharmaceuticals and various other fields. In this context Kim and co-worker [93] represented a metal-free, site-selective C−H alkylation method for diazine N-oxides (**Scheme: I.23**), employing phosphonium ylides. This approach yields a diverse array of alkylated diazine derivatives, demonstrating broad functional group compatibility. The method's efficacy is exemplified through the late-stage functionalization of a readily available pharmaceutical, varenicline. Noteworthy is the sequential C−H alkylation of pyrazine N-oxides, a key step in the total synthesis of the pyrazine-containing natural product paenibacillin A, underscoring the significance of this methodology.



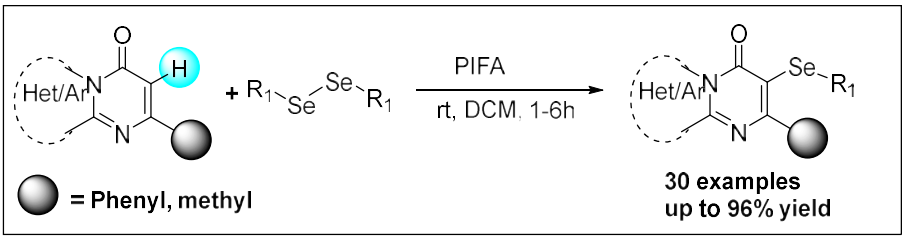
Scheme I.23: C−H alkylation of pyrazin

In 2020 Das et al [94] reported a rapid metal-free C-3 chalcogenation of 4H-pyrido[1,2-a]pyrimidin-4-one has been developed to produce high yields (up to 95%) of diversely orchestrated 3-ArS/ArSe derivative (**Scheme I.24).** This gram-scale reaction, which is operationally straightforward, exhibits broad functional group tolerance and proceeds under mild reaction conditions. Initial experimental research points to a dramatic mechanistic mechanism for these changes.



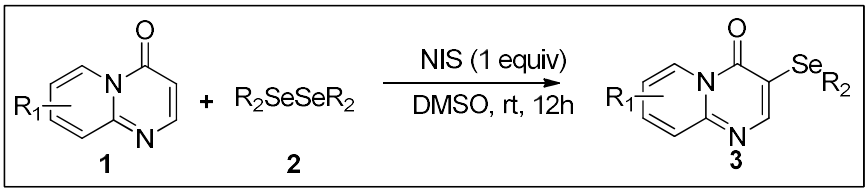
Scheme I.24: Metal free C-3 chalcogenation (selenylation and sulfenylation) of 4*H*-pyrido[1,2-a]pyrimidin-4-ones

In the year 2021, P. Ghosh [95] and colleagues documented the utilization of [Bis(trifluoroacetoxy)iodo]benzene to facilitate the arylselenylation of C-H bonds in 4H-Pyrido-[1,2-a]-Pyrimidin-4-ones, employing easily accessible organodiselenides. (**Scheme: I.25**)With this scalable technique, a wide range of structurally and functionally varied selenoether derivatives has been synthesized with extremely high yields (up to 98%). Interestingly, this approach works in the absence of a metal and at room temperature. It is also shown how this technology can be applied to the simple generation of ArSe substituted 5*H* thiazolo-pyrido[3,2-a]pyrimidin-4-ones



Scheme I.25: PIFA Mediated C-3 Selenylation of Pyrido[1,2-a]Pyrimidin-4-ones at room temparature

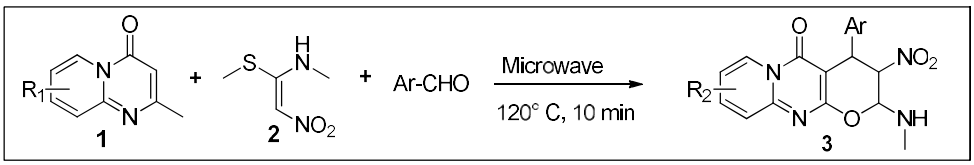
Furthermore, regioselective C3 selenium mediated by metal-free N-iodosuccinimide was devolved by Wang and colleagues in 2021 [1,2-a].-pyrimidin-4-ones 1 and diselenides (**2**) in dimethyl sulfoxide (**Scheme-I.26)** at room temperature [96].



Scheme-I.26: N-Iodosuccinimidemediated regioselective C3 selenylation of 4H-pyrido-[1,2-a]-pyrimidin-4-one

When aryl and alkyl selenium compounds are used corresponding C3 selenyated product of 4H Pyrido-[1,2-a]-pyrimidin-4-formed in presence of (Bis(trifluoroacetoxy)iodo)benzene with excellent yield.

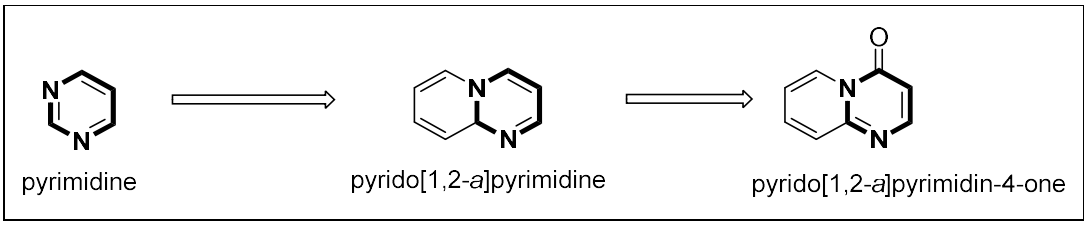
In 2021, Reddy and co-workers developed[97] catalyst free multicomponent reaction of 2-hydroxy-4*H*-pyrido [1,2-a]pyrimidin-4-one(**1**), aromatic aldehydes, and (E)-N-methyl-1-(methylthio)-2-nitroethenamine (**2**) for the synthesis of 4H,5H-pyrano [2,3-d] pyrido [1,2-a] pyrimidin-5-one derivatives (**3**) in good to excellent yields (79–94%) in Monowave 50 reactor (**Scheme I.27]**



Scheme I.27: Metal free decarboxylative ortho C-H aroylation of 2-aryl-pyrido[1,2-a]pyrimidin-4-one.

I.D. Synthetic backgrounds of 4-Pyrimidone

In nature, predominantly nitrogen containing heterocycles are the natural product, synthetic drugs and other biologically active molecules.[98]Therefore, preparation of N-Heterocycles became one of the foremost branch for the synthetic chemist.[99,100]Pyridine frameworks below

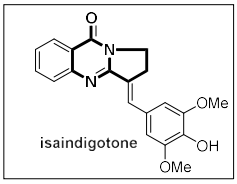
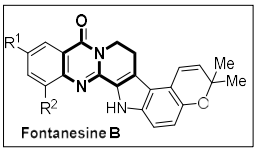
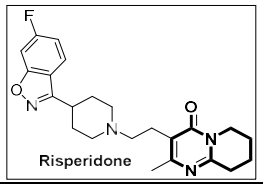
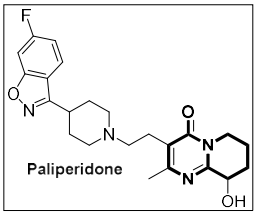
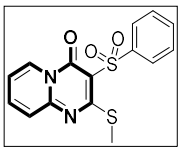
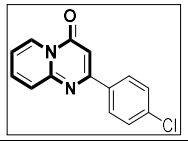


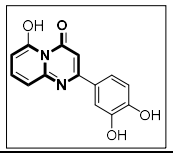
Among the various N-heterocycles, pyrimidine scaffolds (i.e. six-membered diaza-heterocycle) are privileged substructure owing to their biological activity. [101, 102] Numerous natural products as well as the purine bases of RNA and DNA are known to have the pyrimidine motif.[102]

Among pyrimidine derivatives, 4H-pyrido[1,2-a]pyrimidin-4-ones are of great significance due to their prevalence in large number of drugs possessing wide range of biological activities.[103] Many natural products have been isolated from nature containing 4H-pyrido[1,2-

a]pyrimidin-4-one skeleton as a key constituent. For example, pirenperone (Tranquilizer agent)[104], Pemirolast (antiasthmatic)[105], Risperidone[106] and paliperidone (antipsychotic)[107] are a building block of 4H-pyrido[1,2-a]pyrimidin-4-one. Other outstanding skeletal structure include anti-cancer [108], anti-oxidant, anti-depressant, anti-allergicand anti-ulcerative properties.[109] Various new drugs having pyrido-pyrimidinone core are under progress to treat hypertension, tumour, infectious diseases, etc.[110] Few pyrimidone based bioactive molecule are given in table I.1

Table I.1. Bioactive molecule containing 4H-pyrido[1,2-a]pyrimidin-4-one skeleton

S. No.		**References**	**Chemical structure**
1	Anti-mitotic agents	Liu et al. *Org. Lett*. **2005**, *7*, 3363–3366	 isaindigotone
2	Anti-proliferative activity	T. Abe et al. *Helv. Chim. Acta***2019**, *102*, e1900116	 Fontanesine B
3	Anti-psychotics	Nkemjika et al. *J. Nat. Med. Assoc.,114*, **2022**, 621-623	 Risperidone
4	Anti-psychotics	Yang et al. *Bio. Med. Chem.***2017,***25*, 4904–4916	 Paliperidone
5	5-HT6 antagonist	Shuanghua et al. *Bio. Med. Chem.***2014**, *22*, 1782–1790	
6	Anti-cancer,	Guchhait et al. *Eur. J. Med. Chem.***2016**, *122*, 43–54	

7	Anti-oxidant	Motta et al *J. Med. Chem.* **2007**, *50*, 4917–4927	

I.E: Synthesis of 4*H*-pyrido[1,2-a]pyrimidin-4-one skeleton

Owing to their great importance in chemistry, several methods have been reported. First report of 4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylic acid ester synthesis was reported by Lappin in 1948 using 2-aminopyridines with (2-ethoxymethylene)malonic ester and cyclized to the resulting condensed product **5** in boiling diphenyl ether solvent.

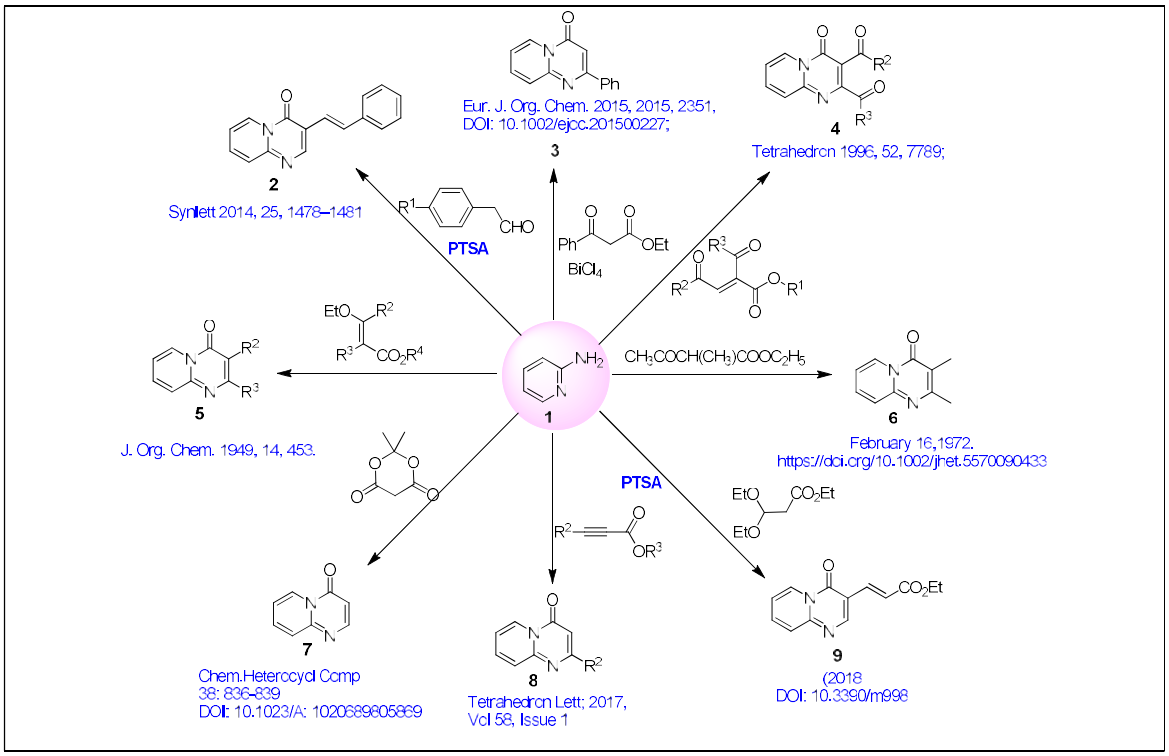
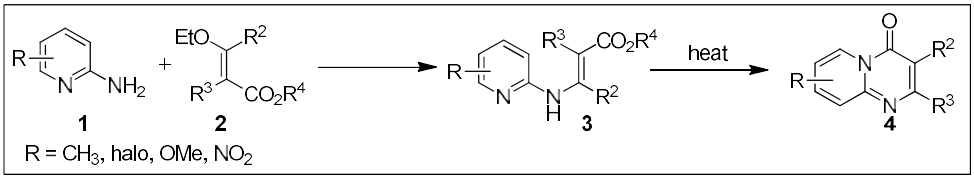


Figure I.10: Various routes for the preparation of 4*H*-pyrido[1,2-a]pyrimidin-4-ones using 2-amino pyridine

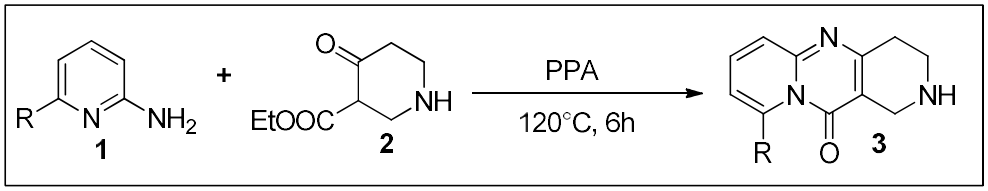
Earlier, synthesis of pyrido-pyrimidin-4-oneframeworks involve reaction of substituted 2-aminopyridine with Meldrum's acid and (hemi)nitriles or nitriles generated various structurally diverged pyrido-pyrimidin-4-one motif**.**

As per report in **1949**[111] scientist Weiss et al prepared 4 pyrimidone using 1 amino pyridine with diethyl ethoxymethylene malonate (EMME) under crypto condition to afforded intermediate-3, which on heating at high temperature resulted of 4-*H*-pyrido[1,2-a]pyrimidin-4-one derivatives in good yield (**Scheme-I.28)**



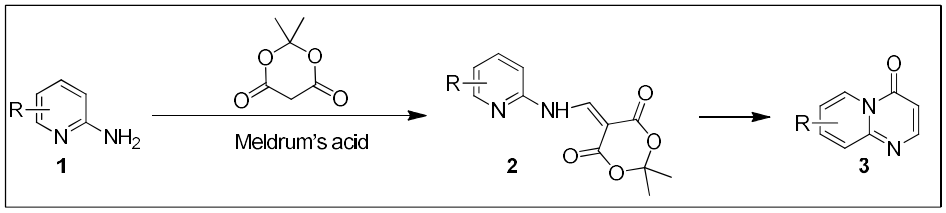
Scheme I.28: General **s**ynthetic scheme for the preparation of 4*H*-pyrido[1,2-a]pyrimidin-4-one using 1,3-bifunctional compounds

The other typical method, involve the reaction of 2-aminopyridines (**1**) with Meldrum's acid (**2**) which results 4H-pyrido[1,2-a]pyrimidin-4-one with excellent (**Scheme I.29)**[112]



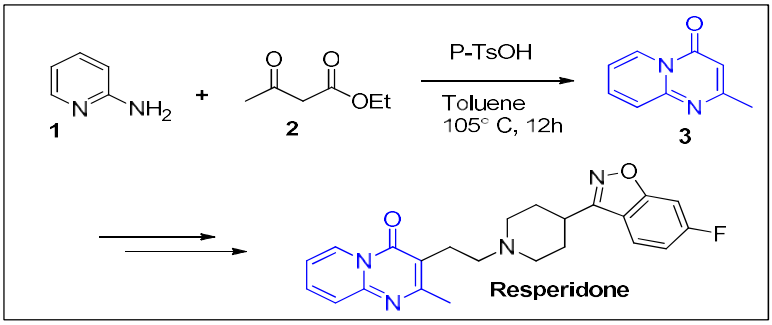
Scheme I.29: General synthetic scheme for 4H-pyrido[1,2-a]pyrimidin-4-one synthesis using PPA

The other typical method, involve the reaction of 2-aminopyridines (**1)** with Meldrum's acid which results 4*H*-pyrido[1,2-a]pyrimidin-4-one via intermediate **(2)**(**Scheme I.30**).[112, 113]



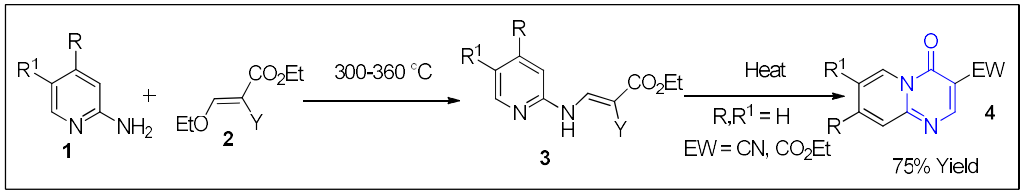
Scheme I.30: General **s**ynthetic scheme for the preparation of 4*H*-pyrido[1,2-a]pyrimidin-4-one using Meldrum's acid

In 2005, Jeong and colleagues [114]successfully prepared 2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one through the reaction of 2-aminopyridine 1 with ethyl 3-oxobutanoate. The synthesis was conducted by heating the reactants in toluene solvent, in the presence of p-toluenesulfonic acid, for 12 hours, resulting in an impressive 95% yield.



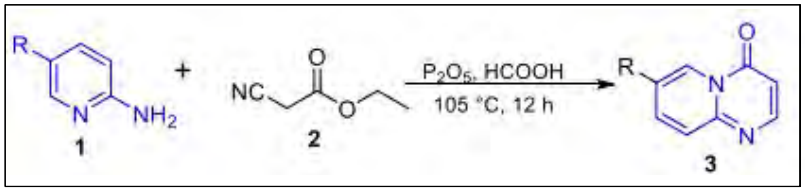
Scheme I.31: Synthesis of 2-methyl-4H-pyrido[1,2a] pyrimidin-4-one using PTSA

In **2012** Dorman and et al [115] described an intramolecular thermal cyclization for the synthesis of pyridopyrimidinones in designed continuous flow reactor system. This reaction was performed at 300-360 °C temperature and under high pressure (100-160 bar) with in very short reactione time (with in 5 mins) in low boiling point solvent (THF) (**Scheme I.31**).



Scheme I.32. Reaction sequence leading to thermal cyclization products

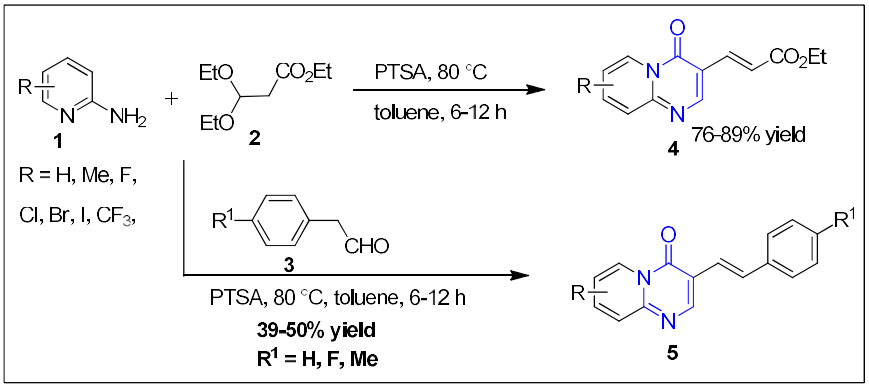
In 2014 Dong and colleagues developed the synthesis of pyrido[1,2-a]pyrimidin-4-one molecules (**3**) using 2-amino pyridine (**1)** and ethyl cyanoacetate(**2**). The reaction conditions include the presence of phosphorus pentoxide and formic acid, with heating at 105 °C for 12 hours. The low to moderate yield was reported in their strudy.



Scheme I.33: Diversity-oriented synthesis of pyrido[1,2-a]pyrimidin4-one compounds

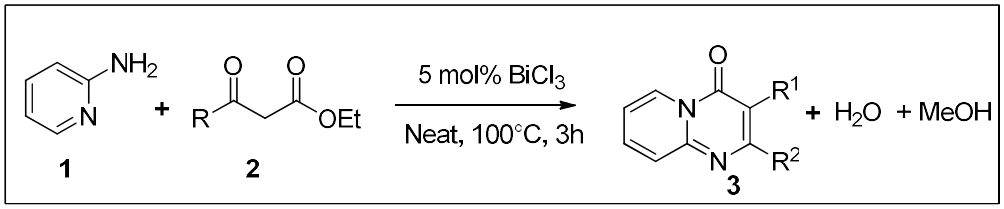
Wang and his co-workers,[117] developed a strategy resulting to the generation of various4H-pyrido[1,2-a]pyrimidin-4-one derivatives (**4**, **5**) by cyclization of various 2-aminopyridine (**1**) and 1,3-bifunctional compound in the presence of PTSA. They also tried the three-component reaction of 2-aminopyridine (**1**), ethyl3,3-diethoxypropanoate (**2**), and 2-phenylacetaldehyde

(**3**) for the synthesis of styryl-functionalized pyrimidin-4-one derivatives **(4)** as the major product (**Scheme I.34**).



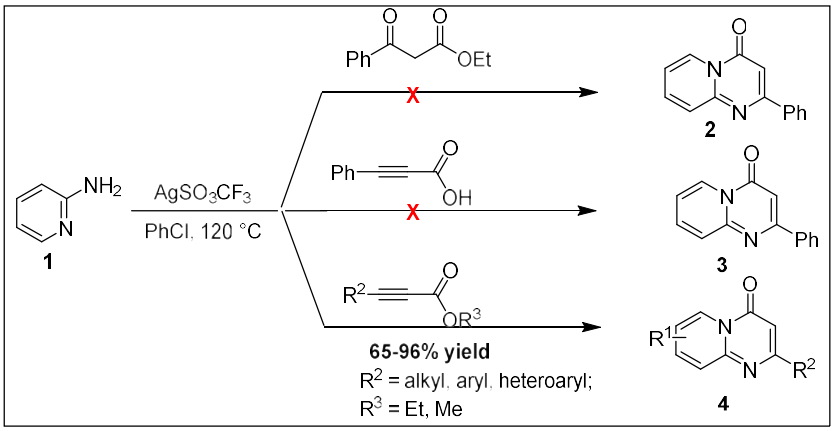
Scheme I.34: Multicomponant reaction for the preparation of 4H-pyrido[1,2-a]pyrimidin-4-one derivatives..

In 2015 Jaenicke and colleagues devised an economical and non-toxic method for the generation of 2-alkyl/aryl-4H-pyrido[1,2-a]pyrimidin-4-ones (9) without the use of solvents, utilizing $BiCl_3$ as the catalyst **(Scheme I.35)** [118]. In this environmentally friendly approach, readily available 2-aminopyridine 1 was subjected to a reaction with β-oxo esters 8, resulting in the formation of the corresponding 2-alkyl/aryl substituted 4H-pyrido[1,2-a]pyrimidin-4-ones (**3**) with excellent yields ranging from 72% to 100%. The synthesis involved a nucleophilic attack of 2-aminopyridine on the $BiCl_3$ complex of β-oxo esters and followed by removal of HCl gas and cyclise to get desired product.



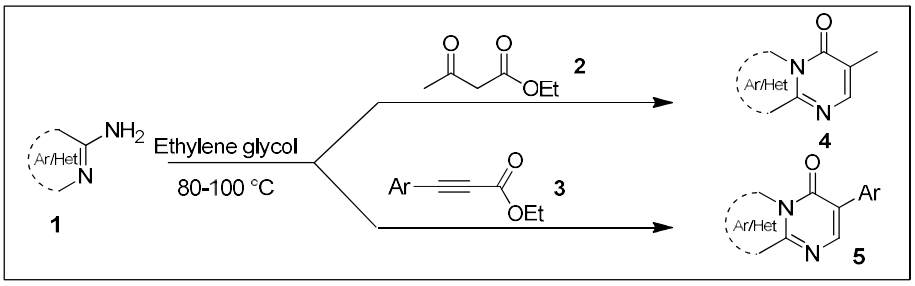
Scheme I.35: Preparation of 4*H*-pyrido[1,2-a]pyrimidin-4-ones using Bi(III) and TsOH-SiO_2 catalyst

Chen and colleagues [119] documented a comparable conversion for producing 4H-pyrido[1,2-a]pyrimidin-4-ones employing a silver catalyst, specifically $AgSO_3CF_3$. This method involved the utilization of alkynoates and 2-aminopyridines as reactants. However, Chen observed that employing phenylpropiolate acid and β-keto esters as reactants did not lead to a successful reaction under the standard conditions (**Scheme I.35**)



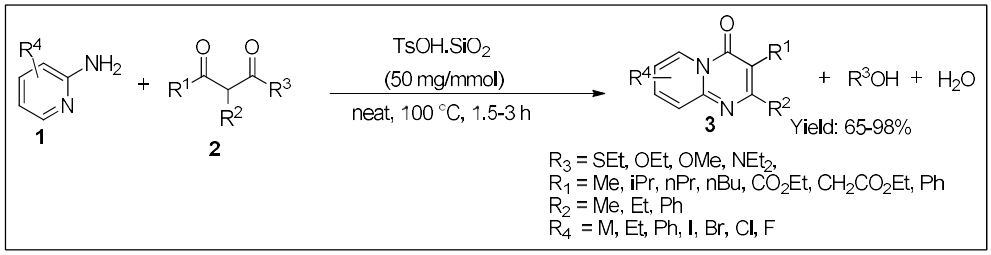
Scheme I.36: Silver mediated preparation of 4H-pyrido[1, 2-a] pyrimidin-4-ones

Similarly in **2020**, Jianhui Liu et al. described a simple and useful protocol for the synthesis of 4*H*-pyrido[1, 2-a] pyrimidin-4-ones derivatives using various 2-amino pyridines and β-oxo ester or alkynoate as reactants in ethylene glycol solvent (**Scheme I.36.**).[120]



Scheme I.37: 4H-pyrido[1,2-a]pyrimidin-4-ones synthesis in ethylene glycol solvent

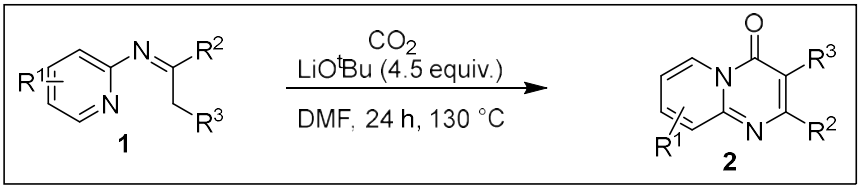
Similarly, In 2019 Yamajala and his co-worker established a green, economical and efficient methodology for the preparation of 4H-pyrido[1,2-a]pyrimidin-4-ones using a TsOH-SiO_2 heterogeneous catalyst.



Scheme I.38: 4H-pyrido[1,2-a]pyrimidin-4-ones synthesis by TsOH on Silica gel

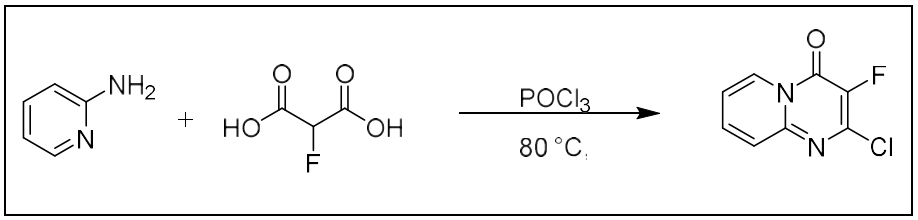
They have also used the readily available starting material 2-aminopyridines/2-aminothiazole/2-aminobenzothiazole and β-oxo esters/β-oxo amides. [121] (**Scheme: I.37**)

In 2020, A novel carbonylation of C(sp3)–H bonds in pyridylamines with one atmosphere of CO_2 is reported [122] to synthesize important pyrimidinones in good yields. This transition-metal-free and redox-neutral process features the use of a nontoxic carbonyl source, broad substrate scope, good functional group tolerance, facile scalability and easy product derivatization.



Scheme I.39: A novel route for the synthesis of pyrimido[1,2-b]pyridazine-4-one using CO_2

In 2021 a group from Sandford has reported[123] employing $POCl_3$ at 80 °C to efficiently synthesise new fluoroheterocyclic scaffolds from easily available 2-fluoromalonate diester and 2-aminopyridine



Scheme I.40: Synthesis of fluorinated pyrimido[1,2-b]pyridazine-4-one from 2-fluoromalonate diester

I.F. Functionalization of pyrimido[1,2-b]pyridazine-4-one via C-H Activation/functionalization:

Currently, C-C and C-X (X = N, S, O, Cl, Br, I, Se, S) bond formations have become a fundamentally imperative tool for synthetic and medicinal chemist.[124]This modern organic synthesis has indispensable application in organic synthesis to explore functionalization to obtain new frameworks with wide therapeutic potency. C-C and C-X (X = N, S, O, Cl, Br, I, Se, S) bond formations are among the most versatile reactions in synthetic chemistry.[125]These methodology has considerably progressed since the development of metal catalysed cross coupling reaction and C-H activation which allow the easy formation of C-C and C-X bonds.[126]Conventional strategies in traditional cross-coupling reactions use functionalized starting materials.There are some reports on the cross coupling of pyrido[1,2-a]pyrimidin-4-ones; few accessible examples of the C-C and C-X bond formation are to be established in the literature. Some examples could be found for introduction of an alkenyl or (het)aryl substituent

into positions C(2),[127]C(3),[128] C(7)[129, 130] of the 4H-pyrido[1,2-a]pyrimidin-4-one centre via C-H activation. Since, C3 arylated pyrido[1,2-a]pyrimidin-4-one showed various biological activities. Therefore, we have set out to investigate the C-H functionalization of the 4H-pyrido[1,2-a]pyrimidin-4-one motif at C-3 position.[108-135]

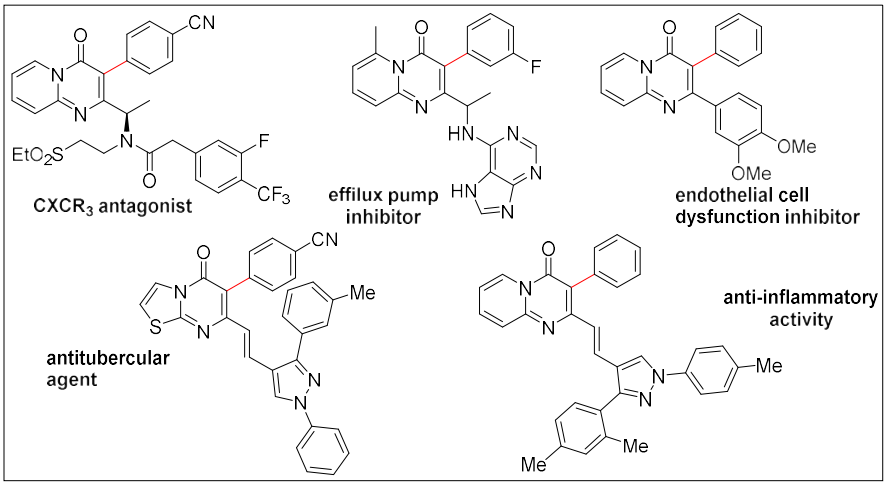
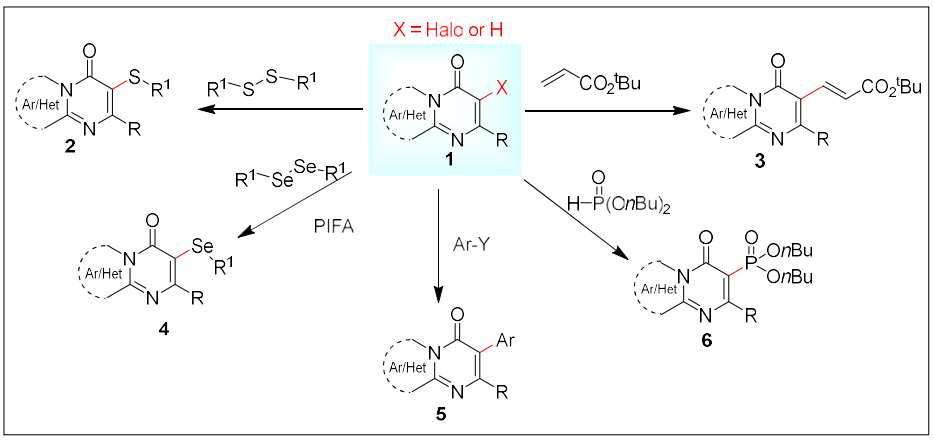


Figure I.11. Important biological active C3 arylated 4H-pyrido[1,2-a]pyrimidin-4-one molecules

There are many reports are in literature having different types of funtionalized group at C-3 position of 4H-pyrido[1,2-a]pyrimidin-4-one. For example C-3 alkenylation[131], C3 arylation[132]C3 phosphonation[133],Aryl selenylation[134], Sulfenylation[135].



Scheme I.41. Different types of C-H functionalization at C3 position of pyrimido[1,2-b]pyridazine-4-one

I. G: Conclusion:

a) On the basis of comprehensive study on 4 pyrimidone and its desrivatives in pharmacological and medicinal chemistry I decided to conisider this topic in my research work.

b) Important components in diverse families of drugs such as anti-bacterial, antiviral, anti-malarial, anti-cancer, anti-tumor, and anti HIV agents