A review on chemistry and synthesis of quinazolines and pyrimidines

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ABSTRACT

Heterocyclic compounds has become a significant role in human life due to the different uses of these compounds. This type of compounds found strong attention among chemists and interested by studying the methods of their synthesis and study their properties. Heterocyclic compounds used in different fields like medicine, pharmacy, agriculture and industry and widely credited for development of human life. Study of these compounds occupies a prominent place in the science of chemistry. Heterocyclic compounds as known it is contain two different types of atoms in their structure so it was great interest in the synthesis and study their chemical, physical characteristics and spectral characteristics. Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical and veterinary products. Heterocycles make up an exceedingly important class of compounds. In fact more than half of all known organic compounds are heterocycles. Many natural drugs such as quinine, palavering, emetine, theophylline, atropine, procaine, codeine, morphine and reserving are heterocycles. Almost all the compounds we know as synthetic drugs such as diazepam, chlorpromazine, ionized, metronidazole, azidothymidine, barbiturates, antipyrine, captopril and methotrexate are also heterocycles. Some dyes, luminophores, pesticides and herbicides are also heterocyclic in nature. One of the main objectives of organic and medicinal chemistry is the design, synthesis and production of molecules having value as human therapeutic agents. There are numerous biologically active molecules with six-membered rings, containing two hetero atoms. The development of research on biological activity of quinazoline compounds started when the compound 2-methyl-1, 3-aryl-4-quinazoline derivative was synthesized. This compound has soporific and sedative action**.** Pyrimidine is a heterocyclic aromatic organic compound similar to benzene and pyridine, containing two nitrogen atoms at positions 1 and 3 of the six-member ring. pyrimidine has many properties in common with pyridine, as the number of nitrogen atoms in the ring increases the ring pi electrons become less energetic and electrophilic aromatic substitution gets more difficult while nucleophilic aromatic substitution gets easier. In this report has been explained different methods synthesis of these compounds and study their spectral properties. I hope to benefit chemists and who interested in studying this type of compounds**.**

Keywords: Quinazoline, pyrimidine,N-heterocyclic, chemistry, synthesis.

INTRODUCTION

Quinazoline is the main six-membered heterocyclic ring system reported for their biological activities, compounds with multiple pharmacophores, which bring together knowledge of a target with understanding of the molecule types that might interact with the target family. Its chemical formula is $C_8H_6N_2$.Molar mass is 130.15 g mol^{-1}. Quinazoline is yellow solid. Robust, versatile and scalable chemistry must be employed to accomplish the task. This characteristic feature of quinazoline would make a good template for a lead generation library. Medicinally it is used as antimalarial agent. It was first prepared by Gabriel in 1903 and first isolated from the Chinese plant aseru. The development of research on biological activity of quinazoline compounds started when the compound 2-methyl-1,3-aryl-4-quinazoline derivative was synthesized. This compound has soporific and sedative action. Derivatives of quinazoline are called quinazolines. Medicinally it has been used in various areas especially as an anti-malarial agent and in cancer treatment. One example of a compound containing the quinazoline structure is mesylate. The ring system is typically prepared by heating 2-acylanilides in the presence of ammonia or amines [1] .Quinazoline derivatives, which belong to the N-containing heterocyclic compounds, have caused universal concerns due to their widely and distinct biopharmaceutical activities. Researchers have already determined many therapeutic activities of quinazoline derivatives, including anti-cancer [2-5], anti-inflammation [6,7], anti-bacterial [7-11], analgesia [6-10], anti-virus [12], anti-cytotoxin [13], anti-spasm [10,14], anti-tuberculosis [15], anti-oxidation [16], anti-malarial [17], anti-hypertension[18], anti-obesity [19], anti-psychotic [20], anti-diabetes [21], etc. Medicinal chemists synthesized a variety of quinazoline compounds with different biological activities by installing various active groups to the quinazoline moiety using developing synthetic methods. And the potential applications of the quinazoline derivatives in fields of biology, pesticides and medicine have also been explored.

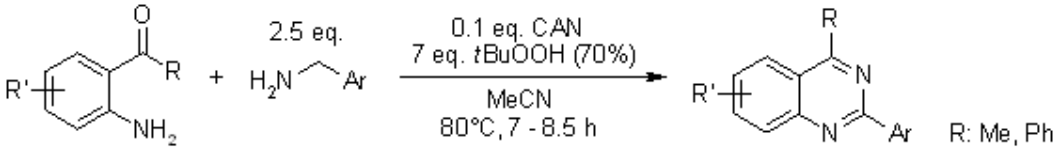
Pyrimidine is a heterocyclic aromatic organic compound containing two nitrogen atoms at positions 1 and 3 of the six-membered ring which shows wide range of biological activities. Its chemical formula is $C_4H_4N_2$.Molar mass is 80.08 g.mol^{-1} . Pyrimidines are synthetically versatile substrates, where they can be used for the synthesis of a large variety of heterocyclic compounds and as raw material for drug synthesis. In medicinal chemistry pyrimidine derivatives have been very well known for their therapeutic applications. Pyrimidine posses wide spectrum of biological activities like including antitubercular [22], antibacterial[23], antifungal[24], antivira[25]l, anti-inflammatory[26], Antimalarial, [27],anticancer[28], anti-HIV activity[29] . Hence the importance of the report for study this type of compounds by methods their synthesis and knowledge of some of its properties to be able to develop in the future. This was the goal of the current report.

Synthesis of quinazolines

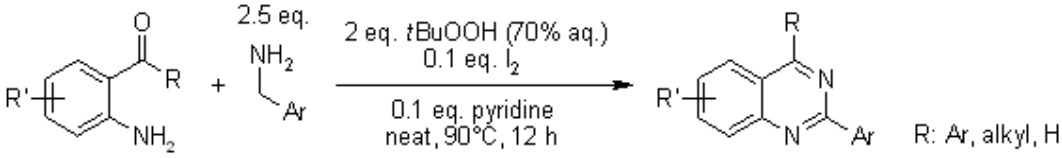
There are many methods to synthesis these compounds, which were synthesized in sixties years of the last century, some of which have been syntheses in the last five years easy ways, and has been studied pharmacy and medical

uses, in this report they are the most common methods in the synthesis of these compounds.

One of these methods uses for the synthesis of 2-phenylquinazolines from 2-aminobenzophenones and benzylamines us catalyzed by ceric ammonium nitrate (CAN)-TBHP in acetonitrile. The product of 2-phenylquinazolines were obtained in good yields, method using 80C^{O} ,7- 8.5 h. and suitable catalyst , which give a good yields for synthesized quinazolines [30] .

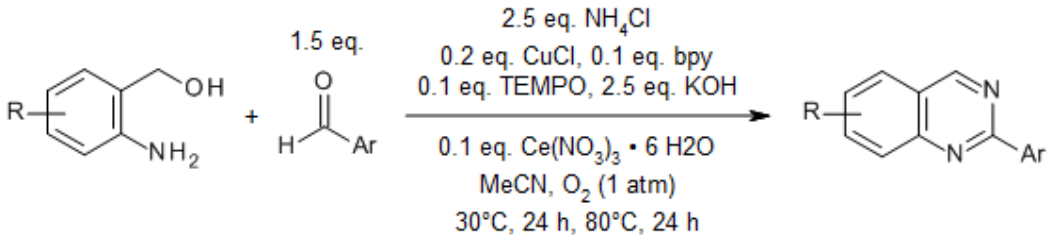


Another method synthesis of 2-phenylquinazolines via a tandem reaction following sp^{3} C-H functionalization. The synthesized compounds of 2-phenylquinazolines were obtained from easily available 2-aminobenzophenones and benzylic amines, using 90C^{O},12h,and 2eq.of t-BuOOH (70%aq) with 1 eq. I_2 . reaction goes with a long time but gives good yields [31] .

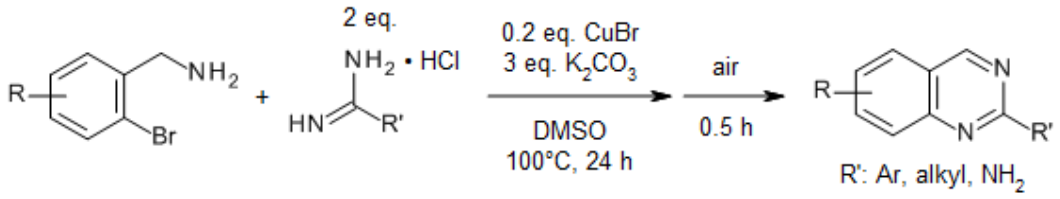


Using copper-catalyzed cascade reaction of (2-aminophenyl)methanols with aldehydes using the combination of cerium nitrate hexahydrate and ammonium chloride leads to a wide range of 2-substituted quinazolines.

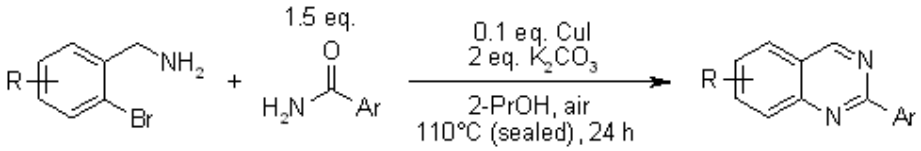
This method using 2.5 eq.from each NH_4Cl and KOH and tolerates a various functional groups and represents a convenient and practical strategy for synthesis of 2-substituted quinazoline derivatives [32] .



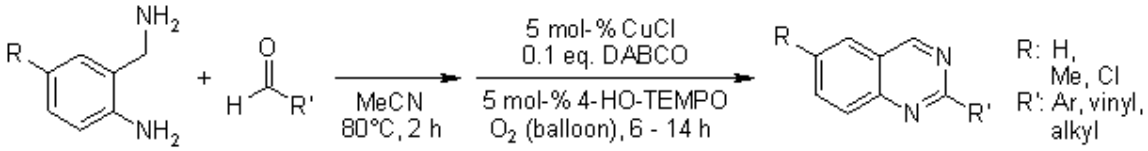
When uses readily available substituted (2-bromophenyl)methylamines and amidine hydrochlorides as the starting materials, inexpensive CuBr as the catalyst, and economical and environment friendly air as the oxidant, 100C^{O},24h, with DMSO as solvent by copper-catalyzed cascade method for the synthesis of quinazolines [33] .



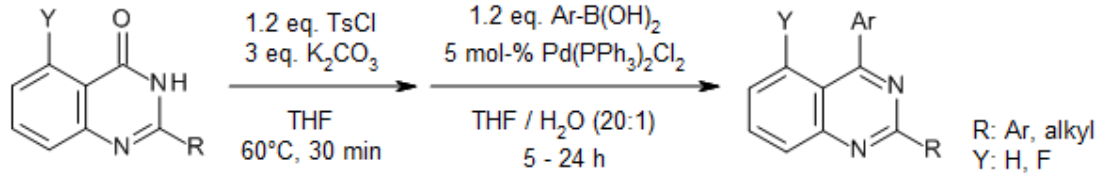
According to this method using readily available substituted (2-bromophenyl)methylamines and amides as starting materials, simple ligand-free copper-catalyzed approach to quinazoline derivatives uses the cascade reaction includes a sequential Ullmann-type coupling and aerobic oxidation and provides a convenient and practical strategy for the synthesis of quinazoline derivatives, using 2eq. of K_2CO_3,1 eq.C_UI,100C^O,24h [34] .



Synthesis of 2-substituted quinazolines and 4*H*-3,1-benzoxazines from the one-pot reaction of aldehydes with 2-aminobenzylamines and 2-aminobenzyl alcohols, using CuCl/DABCO/4-HO-TEMPO as the catalysts and oxygen as the terminal oxidant enabled an efficient aerobic oxidative ,products in good yields can be synthesized have Ar ,alkyl or vinyl groups [35] .

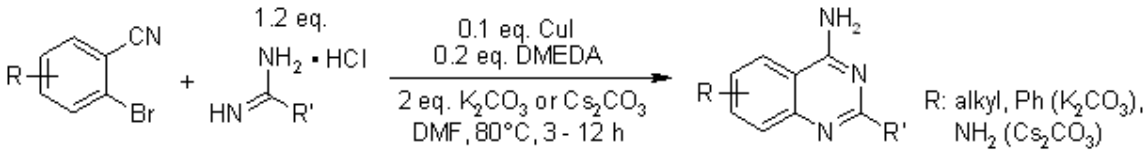


Products of 4-arylquinazolines in good yields is carried out under mild conditions by the palladium-catalyzed arylation of quinazolin-4-ones with arylboronic acids in the presence of TsCl, reaction starting rabid in 30 minutes, then through 24h ,using 1.2 eq Ar-$B(OH)_2$, 5 mol- % $Pd(PPh_3)_2Cl_2$, obtained crystalline products of 4-arylquinazolines [36] .

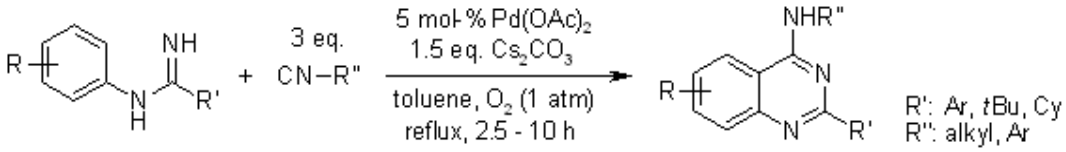


One of an economical and practical method for synthesis of 4-aminoquinazoline and 2,4-diaminoquinazoline

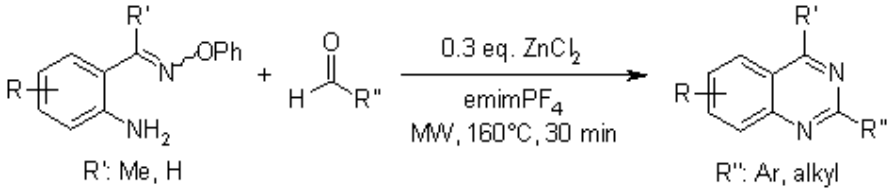
derivatives can also by copper-catalyzed reaction of substituted 2-bromo-benzonitriles with amidines or guanidine, reaction according through 12h, 80C^{O} in good yields of 4-aminoquinazoline and 2,4-diaminoquinazoline derivatives [37] .



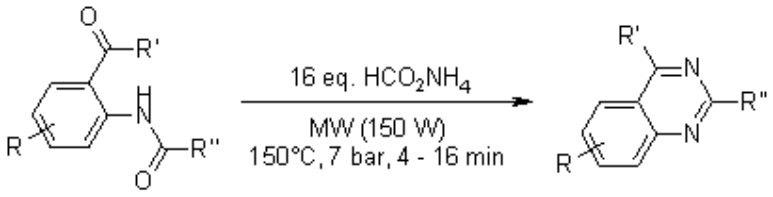
Synthesis of 4-amino-2-aryl(alkyl)quinazolines from readily available *N*-arylamidines and isonitriles via palladium-catalyzed intramolecular aryl C-H amidination by isonitrile insertion. Reaction goes with 5 mol- % $Pd(OAc)_2$ in 1.5 eq CS_2CO_3 ,10 h. Good yields of productions obtained [38] .



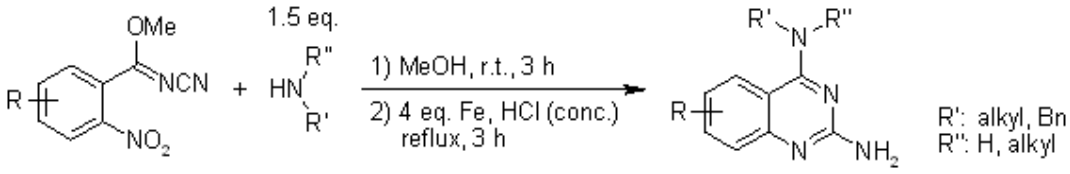
Synthesis of functionalized quinazolines relies on microwave-promoted reactions of *O*-phenyl oximes with aldehydes in the presence of $ZnCl_2$ based on convenient free-radical. Reaction is very rabidly (30min.).It works very well with R: (aryl or alkyl) and heterocyclic aldehydes. Productions in good yields take place for a variety of substituents in the benzenic part of the molecule. Its need 0.3 eq.$ZnCl_2$,160C^{O} [39] .



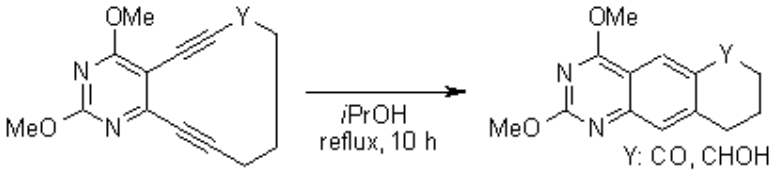
Very fast reaction (nearly 10 min.) can take place a photochemically induced Fries rearrangement of anilides gave several *ortho*-aminoacylbenzene derivatives that were acylated. These acylamides underwent rapid microwave-assited cyclization to 2,4-disubstituted quinazolines (and benzoquinazolines) in the presence of ammonium formate. Products in excellent yields can be obtained, Reaction under oxidation conditions can be conversion in carboxylic of these compounds. [40] .



N -substituted 2,4-diaminoquinazolines products in a high yields obtained as result of condensation of a cyanoimidate with an amine followed by reductive cyclization in an iron-HCl system, Reaction need nearly 3h .When an additional *N*-alkylation can produce two fused heterocycles in a one-pot procedure, Reaction easy occurs with H,alkyl [41] .



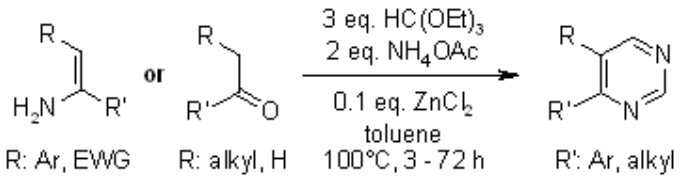
One of the important conversion for this kind of compounds is Bergman cyclization to synthesis new 10-membered pyrimidine enediynes were synthesized in eight steps, respectively. These compounds were compared for their abilities to undergo both thermally and photochemically and to cleave dsDNA under the appropriate conditions, Interaction has a great importance in recent years in the field of pharmacy and medicine [42] **.**



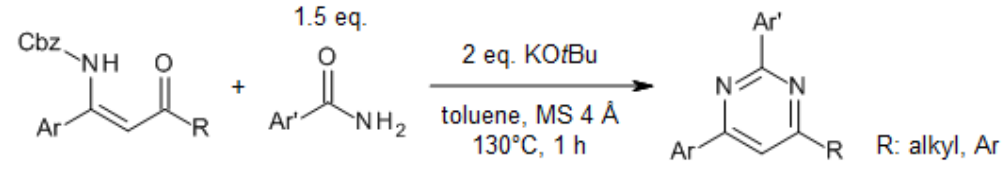
Synthesis of pyrimidines

It seems that the chemistry and methods of synthesis quinazolines easier than pyrimidines. However, there are many methods to synthesizes pyrimidines and their derivatives .In this report there are some of these methods, studded included to their importance**.**

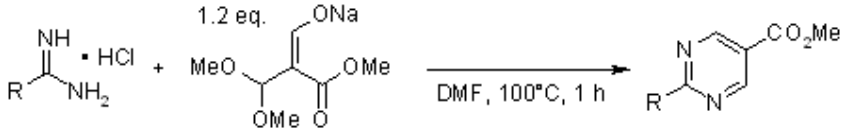
One of known methods is coupling reaction synthesis of various 4,5-disubstituted pyrimidine derivatives in a single step from functionalized enamines, triethyl orthoformate, and ammonium acetate using $ZnCl_2$-as catalyst. The procedure can be successfully applied to the efficient synthesis of mono- and disubstituted pyrimidine derivatives, using methyl ketone derivatives instead of enamines. Reaction easy goes within 3h.Good yields of production have been synthesized and it uses with aryl or alkyl groups [43] **.**



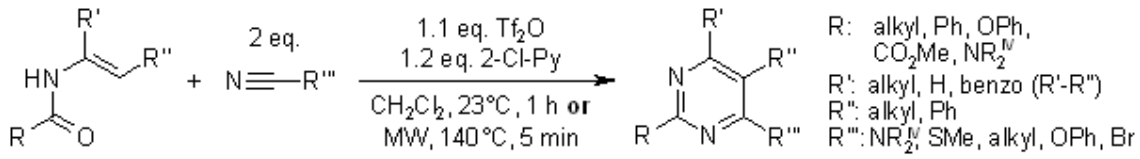
Another method of synthesis is rearrangement of propargylic hydroxylamines allows a highly stereoselective access to Cbz-protected β-enaminones, by NaOH catalyzed. A subsequent synthesis of pyrimidines shows the synthetic potential of these β-enaminones. Reaction uses 2 eq. of KO*t*Bu ,130C^{o},1h.good yields obtained [44] .



Synthesis of 2-substituted pyrimidine-5-carboxylic esters in excellent yields by using sodium salt of 3,3-dimethoxy-2-methoxycarbonylpropen-1-ol in DMF,100C^{O} for 1h, has been found to react with a variety of amidinium salts to afford the corresponding 2-substituted pyrimidine-5-carboxylic esters [45] .

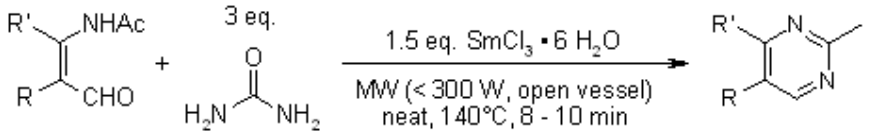


One easy method for synthesis pyrimidines derivatives is direct condensation of cyanic acid derivatives with *N*-vinyl/aryl amides affords the corresponding C4-heteroatom substituted pyrimidines. Use of cyanic bromide and thiocyanatomethane in this chemistry provides versatile azaheterocycles poised for further derivatization. Reaction very rapidly(5min.),140C^{o} in good yields [46] .

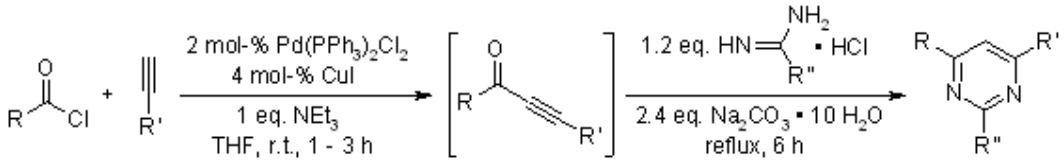


Pyrimidine can be synthesized from β-formyl enamide involves samarium chloride catalysed cyclisation of β-formyl enamides using urea as source of ammonia under microwave irradiation, This is an efficient synthesis

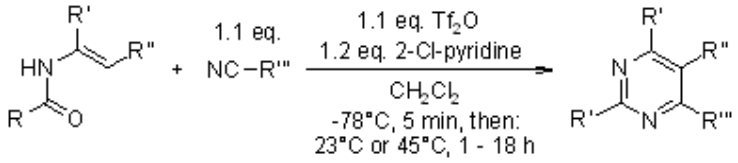
with high yields of pyrimidine through 10min. [47] .



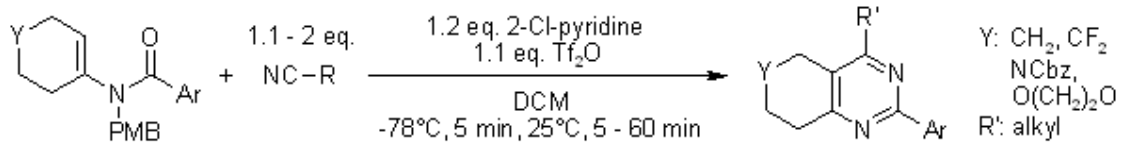
Important method synthesis pyrimidine and its derivatives is coupling of acid chlorides with terminal alkynes using one equivalent of triethylamine under Sonogashira conditions followed by subsequent addition of amines or amidinium salts to the intermediate alkynones allows a straightforward access to enaminones and pyrimidines under mild conditions,RT,3h.THF,good yields of productions were obtained [48] .



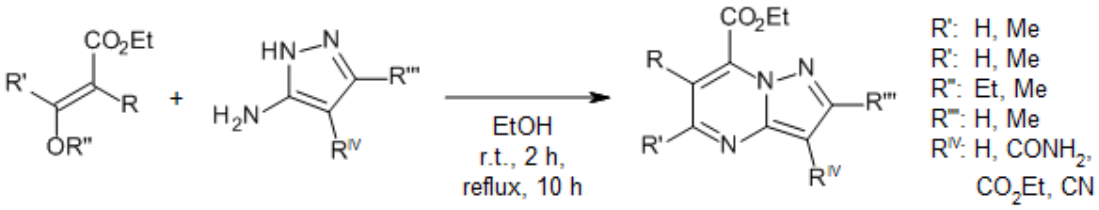
Conversion of various *N*-vinyl and *N*-aryl amides to the corresponding pyrimidine and quinazoline derivatives involves amide activation with 2-chloropyridine and trifluoromethanesulfonic anhydride followed by nitrile addition into the reactive intermediate and cycloisomerization, this reaction is one step and its according with room temprecture,18h.with excellent yields [49] .



Simple and efficient one-pot operation of tetra substituted saturated fused pyrimidines has been synthesized . The strategic utilization of the *N*-PMB group enabled the construction of a broad range of *N*-vinyl tertiary enamide starting materials. This stands as a flexible approach to functionalized pyrimidines with the capability manipulating either ketone, acid chloride, or nitrile reaction partners, Reaction occurs through 5min.,RT,yeildes up to 85% [50] .



Obtained drug-like compounds have a great potential for medicinal chemistry as they closely resemble the structure of several marketed pharmaceuticals The reaction of β,γ-unsaturated γ-alkoxy-α-keto esters with 5-aminopyrazoles proceeds with high regioselectivity to yield new pyrazolo[1,5-*a*]pyrimidines bearing an ester function in the 7-position. Reaction known for pharmacist, its occurs in ETOH,RT,10h in good yield [51] .



Spectral properties of quinazolines:

1) Mass spectroscopy: The spectrum of quinazolines indicates a sequential loss of two molecules of hydrogen cyanide from the molecular ion, the first of which is nonspecific as evidenced by deuterium labeling procedures.

2) Infra red (IR) spectroscopy: The absorption spectra of quinazolines near the 2850Å indicates the presence of the aryl ring , absorption near the 3170Å indicates the presence of N -H stretch and 1690Å indicates the presence of C-N stretch [52].

3) Nuclear magnetic resonance (NMR) spectroscopy: An important feature of this work is that the protonation parameters derived from simple six membered heterocycles can be used to predict chemical shift changes resulting from nitrogen protonation and deprotonation in more complex molecules.δ6.5-8.5 values shows the presence of quinazoline aryl ring [53].

4) 13Carbon NMR: The spectra shows carbon peaks at range of δ50-200. For quinazolines derivatives the range starts from δ115-145.Overlapping is easily confirmed by triplet, doublet peaks obtained. Low intensity peaks show the presence of proton less carbons. So carbonyl group at which position is recognized

Spectral properties of pyrimidines:

1) Mass spectroscopy: The spectrum displayed a large number of vibration peaks, which could be nearly completely assigned through Franck– Condon analysis performed with variations of geometrical parameters at the B3LYP/cc-puts level. Based on the excellent agreement between experimental and calculated results, the definite geometry of the pyrimidine action in the ground electronic state was determined to be a planar structure with *C2V* symmetry with a decreased N–N distance in the ring.

2) Infra red spectroscopy: The absorption spectra of pyrimidines at 10K,the corresponding bands at the 1380-1550A^{O},addition to these fundamental vibrations, several new absorpations were registed,at 1500, 1950,5900 and 3100 A^{O} [54].

3) Nuclear magnetic resonance (NMR) spectroscopy: protonation parameters derived from simple six membered heterocycles can be used to predict chemical shift changes resulting from nitrogen protonation and deprotonation in more complex molecules.6.5-8.5 values shows the presence of pyrimidine ring [55] .

4) 13Carbon NMR: The spectra shows carbon peaks at range of δ50-200. For pyrimidine the range starts from δ110-150.Overlapping is easily confirmed by triplet, doublet peaks obtained. Low intensity peaks show the presence of proton less carbons. So carbonyl group at which position is recognized.

CONCLUSION

Scientific development that the world is witnessing tremendous for this type of compounds makes their study an important. This type of compounds as reported characterized by many features, which make it a place of interest and study. Used in various fields including medical, pharmaceutical, agricultural, industrial and others .report includes several methods for synthesis these compounds that need chemists and pharmacists. This report is useful in obtaining the necessary information to learn methods of synthesis these compounds. Tried to identify the more and important methods to develop new methods with new high efficiency and uses contribute to the development of science and serve humanity. I hope to be successful in this brief report .hope that I have achieved a Target for all.

Acknowledgement :

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