Moroccan Journal of Chemistry

SYNTHESIS AND CHARACTERIZATION OF QUINOLINONES AND BIOLOGICAL ACTIVITY OF SOME SELECTIVE COMPOUNDS

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Received 19 Oct 2015, Revised 04 Jan 2016, Accepted 14 Jan 2016

Abstract:

Quinolinone is a heterocyclic aromatic organic compound. Quinolinone derivatives are having very much usefulness in current therapeutic applications in medicinal chemistry and pharmacology. This compounds having the bicyclic in nature having the fusion of benzene and pyridine the basic moiety present in quinolinones. It is an important pharmacophore and privileged structure in medicinal chemistry. Chromenoquinolinones, isoquinolinones and 4-quinolinones plays a very important role with plenty of useful therapeutic activities such as: antiulcers, antihypertensives, analgesic, anti-inflammatory, anti-virals, antifungals, anticancers, and antihistaminics. The review of the literature shows that the quinolinones derivatives are outstandingly effective compound and number of reviews available for biochemical and pharmacological studies conformed that their molecules are useful against a wide variety of micro-organisms. Because of their importance, the methods for their synthesis have become a focus of synthetic organic chemists. Therefore in the present review we tried to compile the chemistry of different derivative of substituted quinolinones as well as various pharmacological activities and some of the important methodologies used for the synthesis.

Key Words: *Quinolinones, antimicribial, anticonvulsant, pharmacophore*

1. Introduction:

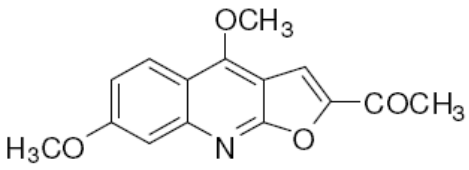
Heterocyclic compounds are those cyclic compounds whose ring contain besides, carbon, one or more atoms of other elements. The non-carbon atoms such rings are referred to as hetero atoms. The most common hetero atoms are nitrogen, sulphur and oxygen. The heterocyclic compounds having lesser common atoms such phosphorus, tin, boron, silicon, bromine, etc. have been a subject of much investigation in recent years. The heterocyclic compounds having three to six carbons in the ring are numerous, but only those having five or six atoms in the ring are by far the most important. Heterocyclic compounds are very widely distributed in nature

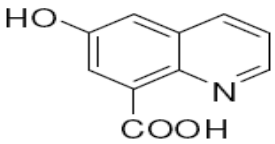
and are particularly important because of the wide variety of physiological activities associated with this class of substances. Several of the important compounds contain heterocyclic rings. The use heterocyclic compounds in field of medicinal chemistry is increasing day by day due to various reasons like heterocyclic compounds are included in the structure of many biochemical materials, which are essential for life. Modern society is also dependent on synthetic heterocycles for use as drugs, The work embodied in this article relates to quinolinone as it is a versatile heterocycle possessing a wide spectrum of biological activities like antifungal, anti-allergic, antimicrobial, antiviral and antineoplastic activities. Although it comprising nearly one quarter of top hundred selling drugs but due to problems like resistance, toxicity, there is a need for minor modification of existing agents and to design novel agents which incorporate quinolinone as pharmacophoric handle which act against new targets. This review highlights the importance of quinolinone in medicinal world along with a few examples of clinically used drugs. Additionally review of some of the work concerning quinolinone reported in the literature has also been provided [1].

2. Results

2.1. Chromenoquinolinones:

Quinolinones are important class of heterocycles with unique biological activities. They are valuable synthetic intermediates and key structural subunits of a variety of natural products in the form of quinolinone alkaloids like 2-acetylevolitrine and 6-hydroxyquinolinone-8-carboxylic acid [2-4]. Quinolinone derivatives represent privileged moieties in medicinal chemistry and possess diverse range of biological activities including antimalarial [5-7], anticancer [8-11], antituberculosis [12-16], antiinflammatory [17-19], anti-Alziemer [20,21] anti-HIV [22-24], anti-HBV [25] anti-HCV [26], antioxidant [27,28], antifungal and antibacterial [29-31]. They are also found in active pharmaceutical ingredients including Cetromycin (antibacterial) [32], Pitavastatin (statin) [33] Montelukast (asthma and allergy) [34] and many antimalarial drugs [35]. They are used as estrogen receptor ligands [36] and also for the treatment of estrogen dependent diseases [37]. Quinolinone derivatives also act as potent liver X receptor (LXR) agonists [38-41]. They also find applications in agrochemicals and effect chemicals such as dye stuffs and corrosion inhibitors [42].



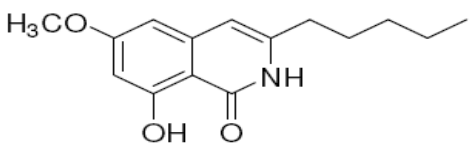


2-Acetylevolitrine (antiplatelet aggregation) ***6-OH-quinolinone-8-carboxylic acid (Antifungal)***

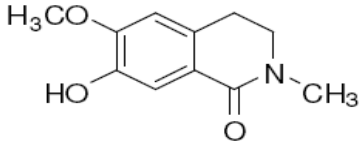
Differently fused chromenopyridin-5-ones are also under study due to their biological activities [43]. Some of them make the backbone of naturally occurring alkaloids, for example, of Santiagonamine [44]. Several chromeno[4,3-*b*] pyridin-5-ones, both natural and non-natural products are currently under clinical trials [45-46] and have attracted much attention in the recent years. The related 6*H*-chromeno[4,3-*b*]quinolinones have also been studied in medicinal chemistry, such as a new series of estrogen receptor β-selective ligands [47-48] The attachment of fluorine-containing functional groups to biomolecules often leads to the development of new physiologically active compounds [49-51]. Langer group has some recent achievements [52-55] related to the synthesis of fluorinated drug like scaffolds.

2.2.Isoquinolinones:

Isoquinolone derivatives are important class of heterocycles with unique biological activities. The Isoquinolone ring system is found in many natural products especially plant alkaloids like ruprechstyril and thalifoline [56,57]. They have many biological activities like anticancer [58,59], JNK inhibitors [60-62] for the treatment of diabetes, cancer, inflammation, stroke etc, Rho-kinase inhibitors [63-65] for the treatment of diabetes, neurodegenerative diseases and cancer and non-peptide dipeptidyl peptidase IV inhibitors [66] for the treatment of diabetes.



Ruprechstyril

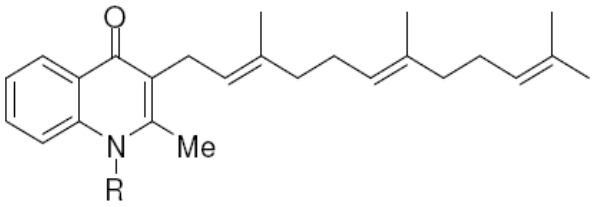


Thalifoline

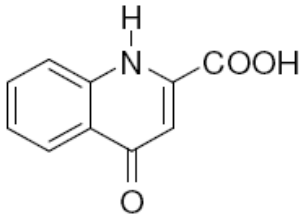
Thiophene is considered to be bioisostere of benzene ring [67] and can be used for fine tuning of properties of potential drug molecules. Both aromatic rings are similar in size (isostere) and electronic properties. The diameter of sulfur atom is roughly equivalent to the distance between two neighboring carbon atoms in benzene. The physiological effects of thiophene are similar to those of benzene (bioisostere), with frequent superior phamacodynamic, pharmacokinetic, or toxicological properties. Thienopyridine derivatives have many biological properties such as potent CHK1 inhibitor [68] and c-Src inhibitors [69] for cancer therapy. Ticlopidine (trade name Ticlid) and Clopidogrel (trade names Plavix and Clopilet) are two antiplatelet drugs derived from the thienopyridine skeleton, often used in the treatment of coronary artery disease, peripheral vascular disease and cerebrovascular disease [70]. Similarly thienopyridinone derivatives also have found various biological applications as potent GSK 3b inhibitor [71] for the treatment of neurodegenerative diseases such as Alzheimer and neurological diseases such as bipolar disorders, as potent CDC7 inhibitors [72] for cancer therapy and as a cytoprotectant.

2.2.The 4-Quinolinones:

Quinolinones represent one of the most important class of nitrogen containing heterocycles. They are found in a large number of natural products many of which are biologically active like Aurachin C and Transtorine [73-76].



Aurachin C (R=OH) Aurachin D (R=H) (antiplasmodial)

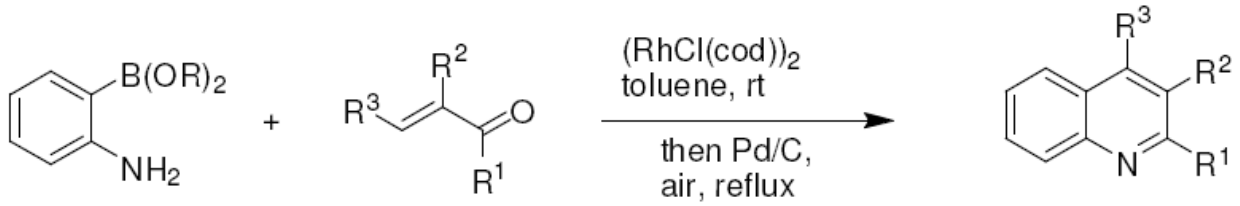


Transtorine (antibacterial)

Quinolinones are also integral to a large number of synthetic compounds with activities including anticancer [77-80], anti-HIV [81-84], anti-HCV [85-87], antioxidant [88], antiinflammatory [89], antimalarial [90] and anti-depressant [91]. They also represent an important category of antibacterial agents [92-94] and some show antimycobacterial activities [95-97]. They also act as potential agents for the treatment of Alzheimer disease [98]. They also act as selective androgen receptor modulator [99,100] and as selective human neuronal nitric oxide synthase inhibitors [101,102]. They also show cardiac stimulant [103] and diuretic activity [104].

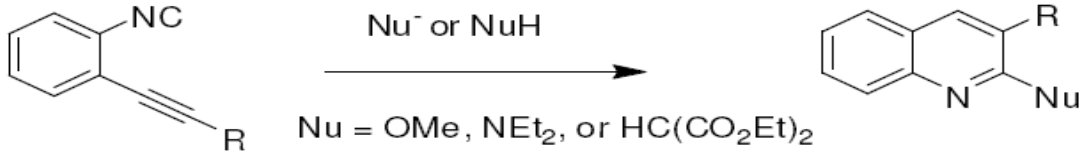
2.3.Synthetic methods of Chromenoquinolinones:

A number of strategies have been devised for the synthesis of quinolinone ring system. A convergent, regiospecific two component synthesis of quinolinones from a,b-unsaturated ketones and *o*-aminophenylboronates [105].



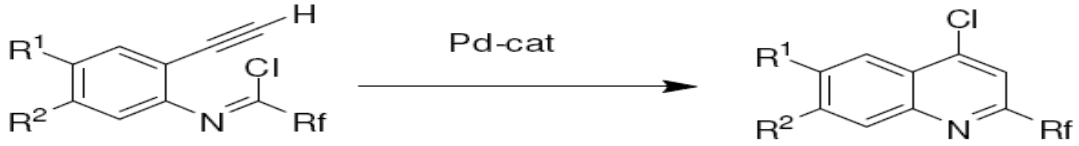
R_1= Me, Ph, 4-$MeOC_6H_4$, 1-napthyl, 3-thienyl, 2-pyridyl; R_2= H, Me
R_3= H, C_5H_{11}, Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$

A method for the synthesis of 2,3-disubstitued quinolinones through nucleophile triggered cyclization of *o*-alkynylisocyanobenzenes [106].



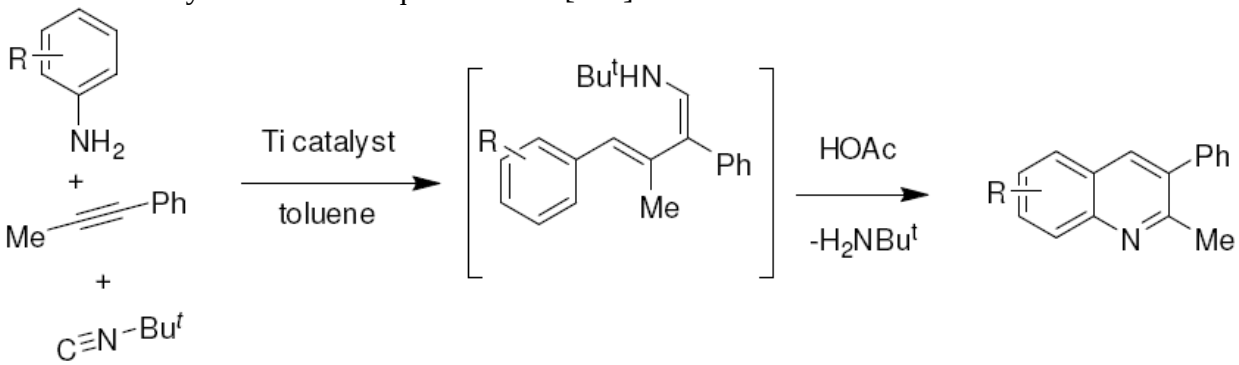
Nu = OMe, NEt_2, or $HC(CO_2Et)_2$; R= *t* -Bu, *c*-Hex, CH_2OCH_3, Ph

Synthesis of 4-chloroquinolinones via palladium-catalyzed chloroimination of imidoyl chlorides to a triple bond. This Pd-catalyzed chloroimination reaction expands the scope of palladium chemistry [107].



R_1= H, Cl, F, CO_2Et; R_2= H, F; Rf= CF_3, C_3F_7, CF_2Cl, CHF_2

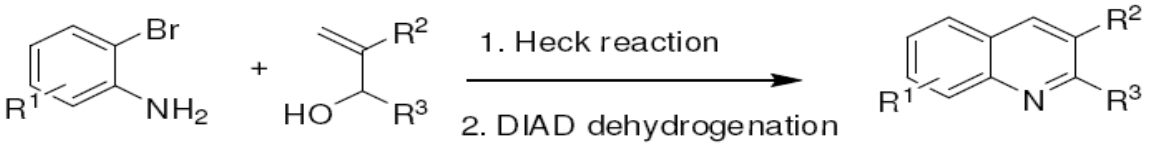
A titanium-catalyzed three-component coupling reaction for direct access to substituted quinolinones. The primary amines employed can be substituted anilines, aminonapthalenes, or even heterocylic amines, which leads to a variety of substituted quinolinones [108].



Synthesis of quinolinones via palladium(0)-mediated Ullmann cross-coupling of 1-bromo-2-nitroarenes with b-halo-enals and then reaction with dihydrogen in the presence of Pd on C. This synthesis highlight the utility of Pd(0)- mediated Ullmann cross-coupling in the synthesis of heterocycles [109].

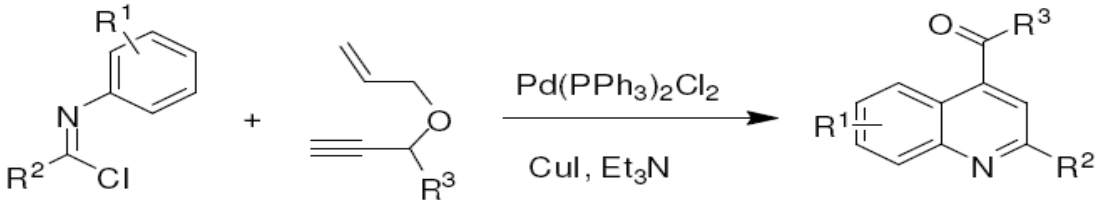
R= H, OMe n=1,2,3

One-pot synthesis of substituted quinolinones via a Heck reaction of 2-bromoanilines and allylic alcohols followed by dehydrogenation with diisopropyl azodicarboxylate (DIAD) [110].



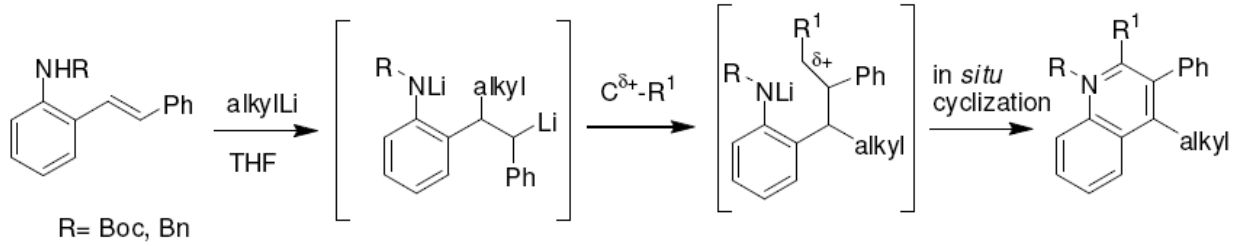
R_1= H, 2-F, 3-F, 4-F, 2,4-F; R_2= H, Me ; R_3= Me, Et, *t*-Bu, *n*-Bu, Ph

A domino reaction for the synthesis of quinolinones via palladiumcatalyzed Sonogashira coupling of benzimidoyl chlorides with 1,6-enynes and then cyclization. The procedure is simple, rapid and general, and the substrates are readily available [111].

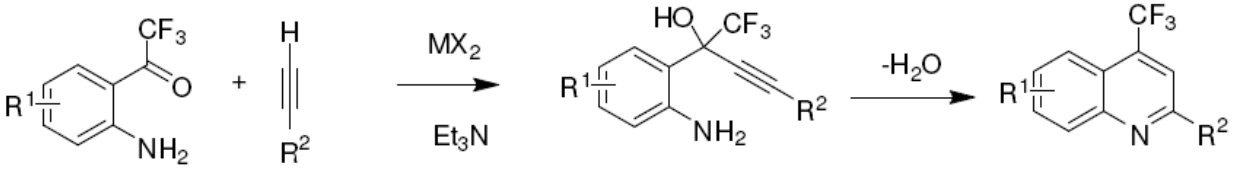


R_1= H, 4-Me, 4-OMe, 4-Cl; R_2= Ph, 4-MeC_6H_4, 4-ClC_6H_4;
R_3= Ph, 4-MeC_6H_4, 4-OMeC_6H_4, 4-ClC_6H_4

The carbolithiation /electrophile reaction methodology for the synthesis of quinolinones [112].

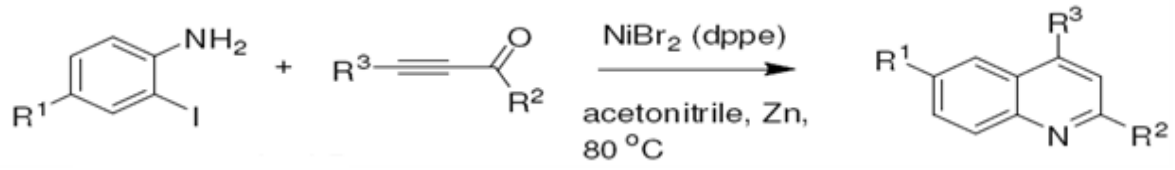


One pot synthesis of 4-triflouromethyl-substituted quinolinone via zinc-mediated alkynylation-cyclization of o-trifluoroacetyl anilines. The salient features of the procedure are facile synthesis under mild conditions and rapid access to a wide range of functionailzed 4-trifluoromethylated quinolinones [113].



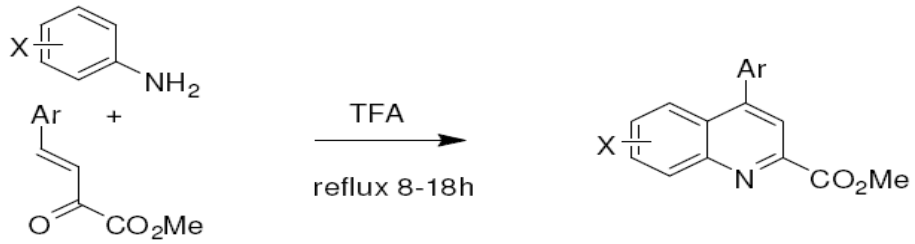
R_1= *p*-Cl, *p*-MeO, *o*-MeO, H, *p*-CF3; R_2= Ph, *c*-C_3H_5

An efficient and convenient route to 2,4-disubstituted quinolinone synthesis by nickel catalyzed cyclization of 2-iodoanilines with aroylalkynes. The reaction can be employed for the synthesis of naturally occurring quinolinones derivatives in good yields [114].



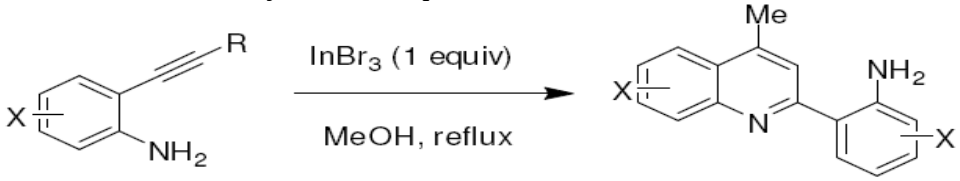
R_1= H, Me, Cl, CF_3; R_2= Ph, Me; R_3= Ph, *n*-Bu, Et

A reversal of the regiochemistry of the Skraup-Doebner-Von Miller quinolinone synthesis when anilines were condensed with g-aryl-b,g-unsaturated a-ketoesters in refluxing TFA [115]



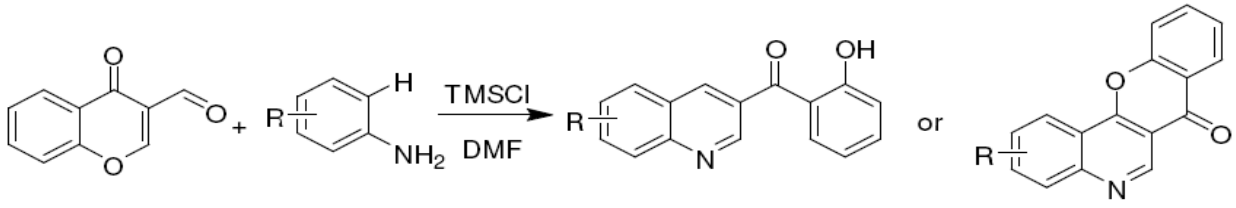
X= H, 4-OMe, 4-Me, 4-F, 4-NO_2

The synthesis of polysubstituted quinolinones by InBr3-promoted dimerization of 2-ethynylaniline derivatives. This is the first direct synthesis of quinolinones skeleton via dimerization of identical molecules [116].



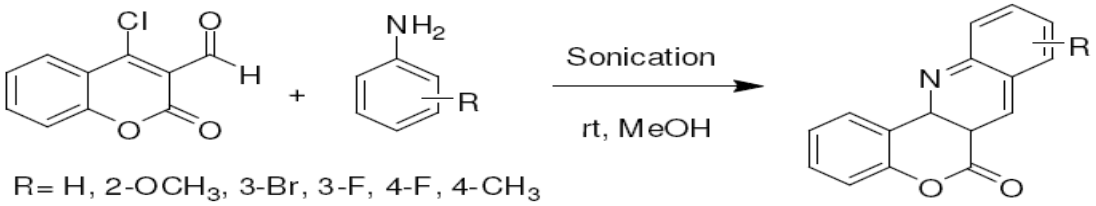
R = H, or $SiMe_3$

A facile synthesis of quinolinones based on TMSCl-mediated recyclization of 3-formylchromone with various anilines. TMSCl acts as a promoter and water scavenger.The developed procedure can be applied for the synthesis of diverse sets of functional drug like quinolinones [117].



R= 4-F, 4-Me, 4-CF3, 4-Cl, 4-NO_2

Ultrasound-promoted catalyst free synthesis of 6*H*-1-benzopyrano[4,3-*b*]quinolinones-6-one via the reaction of 4-chloro-2-oxo-2*H*chromene-3-carbaldehyde with anilines. Many of the compounds were found to be active for anti-proliferative properties [118].

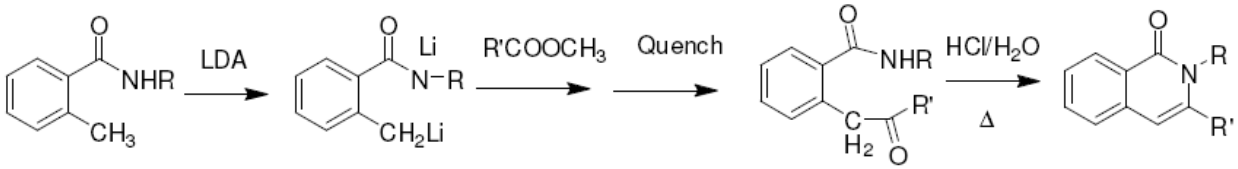


R= H, 2-OCH_3, 3-Br, 3-F, 4-F, 4-CH_3

R= H, 2-OCH_3, 3-Br, 3-F, 4-F, 4-CH_3

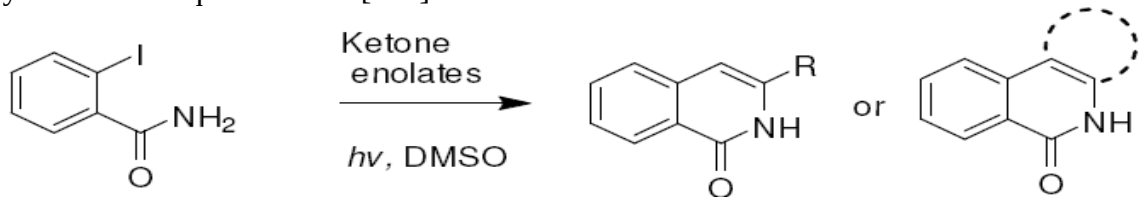
2.4.Synthetic methods of Isoquinolinones:

A number of strategies have been developed for the synthesis of isoquinolinones. Some of the strategies are as follows: synthesis of isoquinolinones via double lithiation of arylbenzamides and the resulting polyanion-type intermediate were condensed with aromatic esters followed by acid cyclization [119].

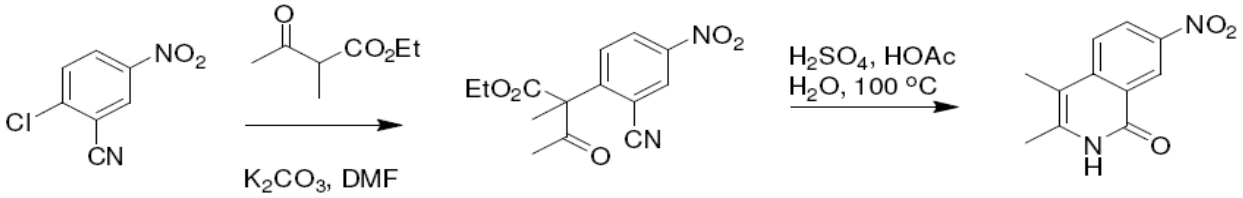


R= -Ar, -CH_2Ar, or -$N(CH_3)_2$ R'= Phenyl or subst. Phenyl

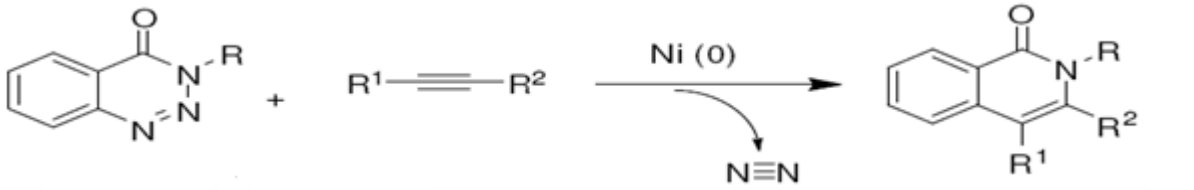
Synthesis of isoquinolinones and fused isoquinolinones via photostimulated SRN1 reaction of 2-iodobenzamide with enolates of aromatic, aliphatic and cyclic ketones in DMSO. Due to the availability of the starting materials and mild conditions of the procedure, this methodology can be used as a general method for the synthesis of isoquinolinones.[120].



A versatile method for the synthesis of isoquinolinone via reaction of 2-chlorobenzonitriles with b-ketoesters in an SNAr reaction. The compounds have been shown to possess kinase inhibitor activity [121].

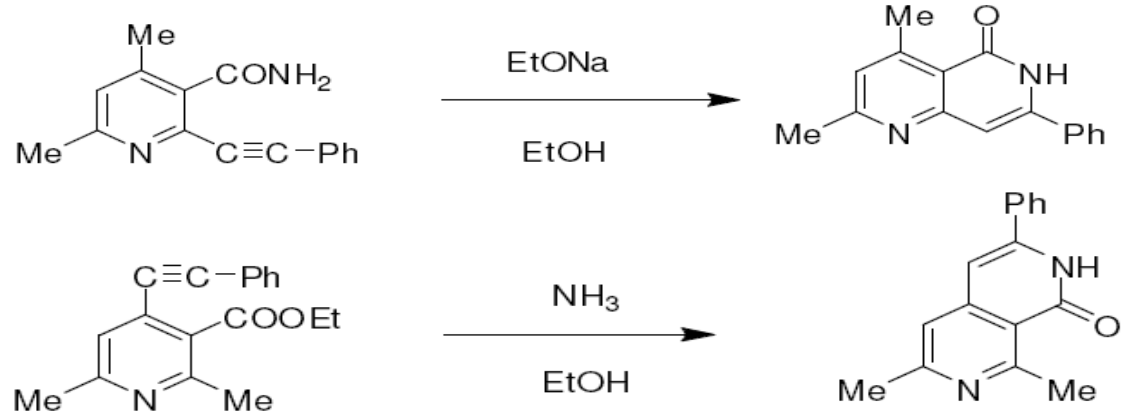


The facile synthesis of isoquinolones in high yields by reaction of 1,2,3-benzotriazin-4(3*H*)-ones with terminal alkynes in the presence of nickel(0)/phosphine catalyst. A wide range of alkynes were regioselectively incorporated into 1,2,3-benzotriazin-4(3*H*)-ones with loss of a nitrogen molecule [122].

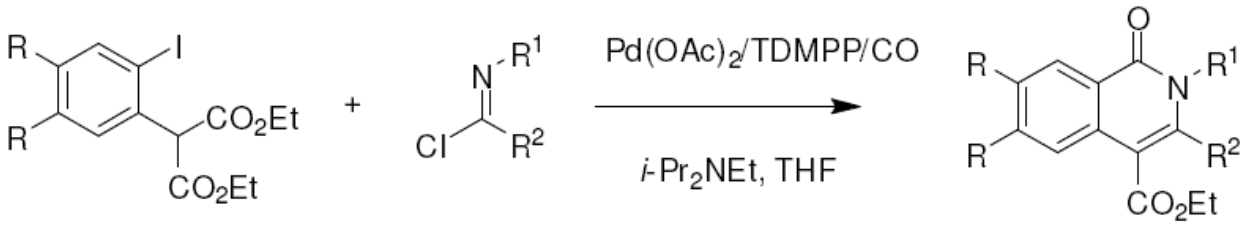


R= H, Me, Bn, subst-Ph; R_1= Me, *i*-Pr, *n*-Bu, Ph, TMS; R_2= Me, CO_2Et, Ph, subst-Ph

Synthesis of napthyridine derivatives by cyclization of pyridinecarboxamides having an ethynyl group adjacent to the carbamoyl group. The synthesis of the starting pyridine derivatives were easily accomplished by crosscoupling of the corresponding halopyridines with acetylenes [123].

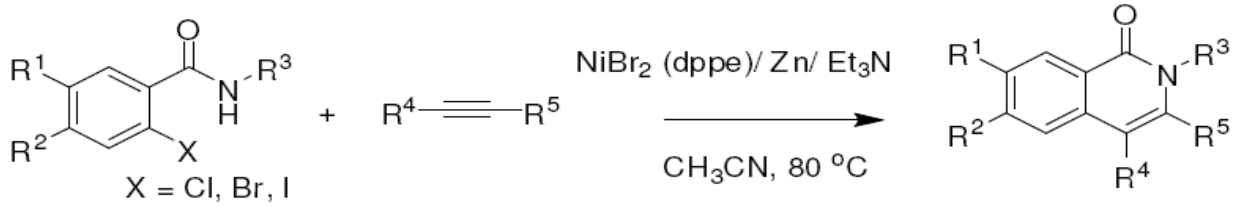


An efficient route to substituted isoquinolones via palladium catalyzed carbonylation decarboxylation of diethyl(2-iodoaryl)malonates with imidoyl chlorides. The reaction is compatible with a variety of functional groups and affrods isoquinolinones in good yield [124].



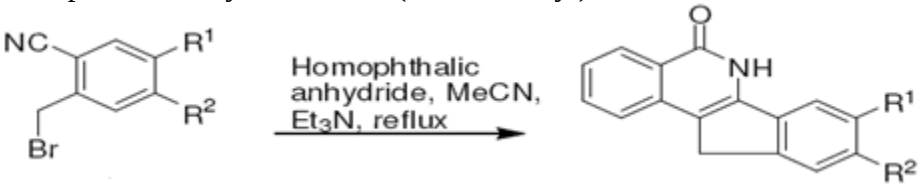
R= H, OMe; R_1,R_2= Ph, subst-Ph, alkyl

An easy and convenient method for the synthesis of highly substituted isoquinolones by nickel-catalyzed annulation of substituted 2-halobenzamides with alkynes. This protocol is successfully applied to the total synthesis of oxyavicine with excellent yield [125].



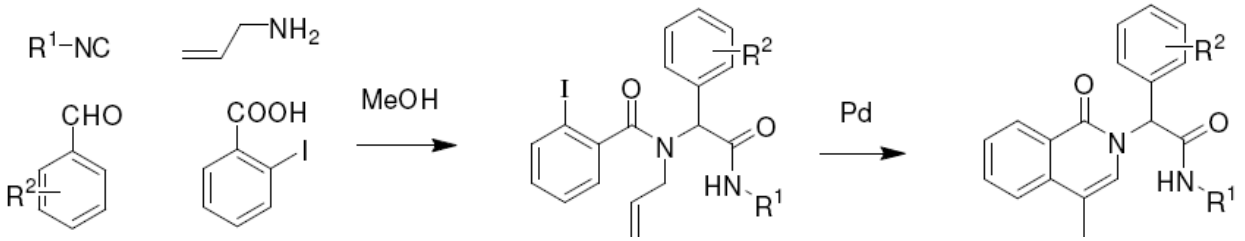
X = Cl, Br, I; R_1,R_2= H, Cl, OMe ; R_3= H, Me, Allyl, propyl; R_4,R_5= H, Ph, *n*-Pr, CH_2OMe

A facile and convenient synthesis of substituted isoquinolinones by the base-promoted condensation reaction of homophthalic anhydride and 2-(bromomethyl)-benzonitrile [126].



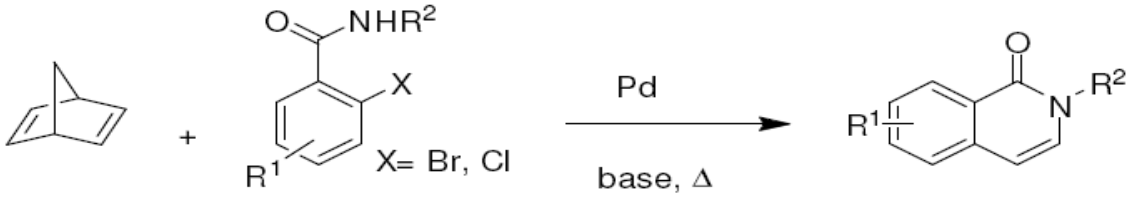
R_1,R_2 = H, F, NO_2

A concise synthesis of isoquinolinone via the Ugi fourcomponent reaction and then palladium-catalyzed intramolecular Heck reaction. This two step synthetic route allows easy synthesis of a varity of isoquinolinones [127].



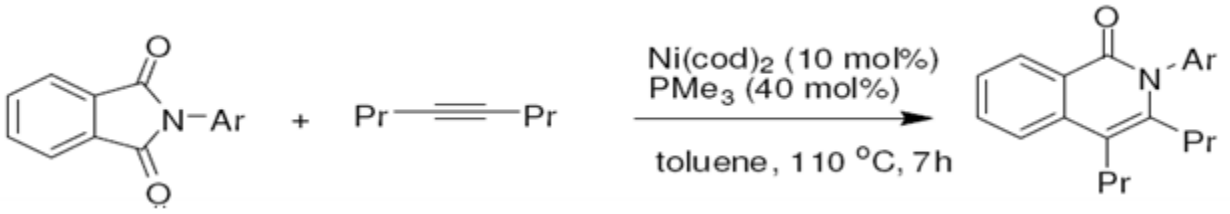
R_1= *t*-Bu, *c*-Hex; R_2= 4-NO_2, 4-Cl, 2-NO_2, 4-OMe

An effencient route to the synthesis of functionalized isoquinolinones in good yields via palladium-catalyzed annulation of substituted halobenzamides with norbornadiene [128].

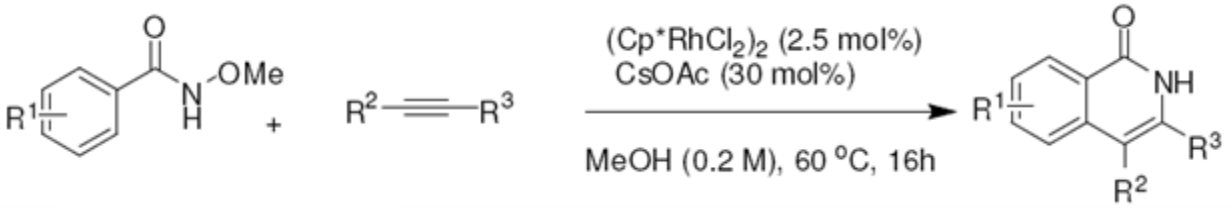


R_1= Me, OMe, *di* -OMe, NO_2, *di* –Cl; R_2= Ph, Bn; X= Br, Cl

A synthesis of substituted isoquinolinones via nickelcatalyzed decarbonylative addition of phthalimides to alkynes [129].

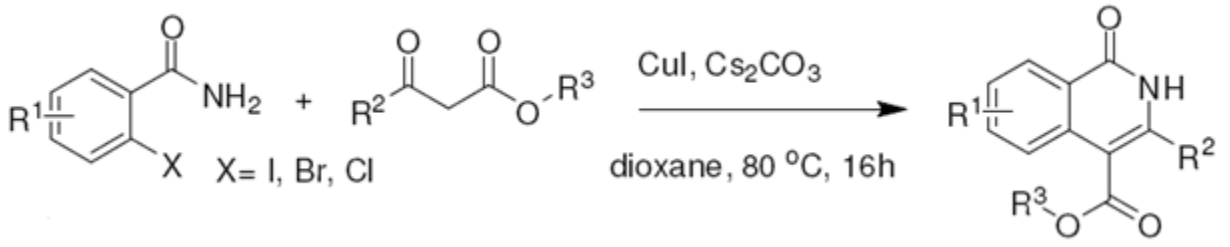


Synthesis of isoquinolones via rhodium-catalyzed reaction. This synthesis operates under mild conditions, and is not sensitive to air or moisture [130].



R_1= H, OMe, NO_2, CF_3 R_2= Ph, Me, *n*-Pr, *n*-Hex R_3= Ph, Py

An efficient one-pot copper-catalyzed method for the synthesis of substituted isoquinolones via cascade reactions of substituted 2-halobenzamides with b-keto esters under mild conditions [131].

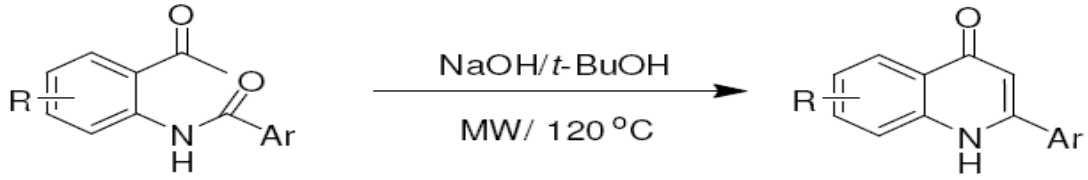


X= I, Br, Cl

R_1= H, Me, OMe, Cl R_2= Me, *n*-Pr, *iso*-Pr R_3= Et, *t*-Bu

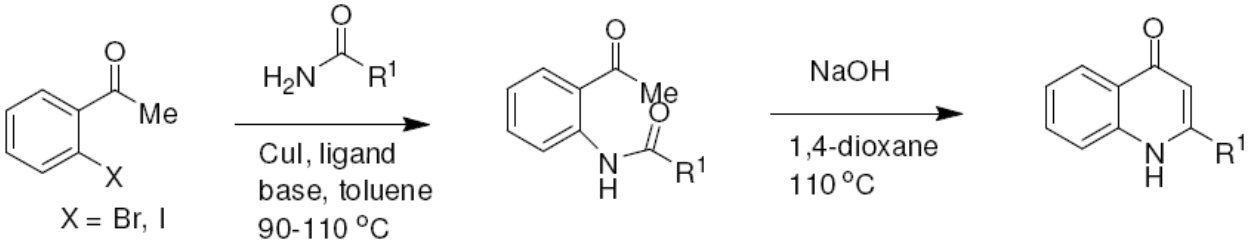
2.5.Synthetic methods of 4-Quinolinones:

Many methods have been developed for the synthesis of 4-quinolinones. The most widely used method for the synthesis of 4-quinolone is base promoted cyclization of N-(ketoaryl)-amides (Camps cyclization). The microwave assisted synthesis of 4-quinolones by exposing corresponding acylated 2-aminoacetophenone to microwave irradiation in the presence of NaOH. This is a rapid and straightforward method giving 4-quinolones in high yields [132].



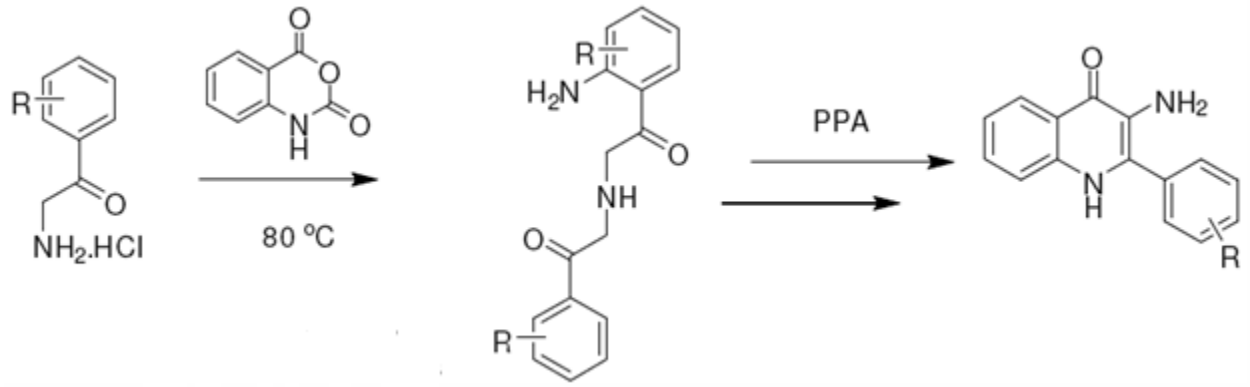
R= H, 4-Cl, 4,5-OMe, 3,4,5-OMe

A direct two step method for the synthesis of 4-quinolones involving Cu-catalyzed amidation-base-mediated Camps-cyclization. With CuI, a diamine ligand, and base as the catalyst system, the amidation reactions proceed in good yields for a range of aryl, heteroaryl, and vinyl amides [133].



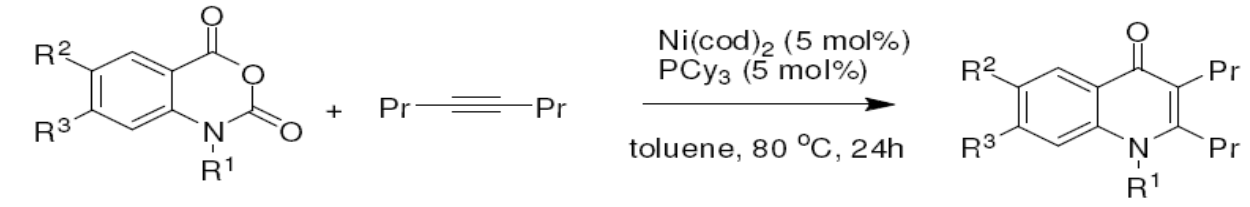
X = Br, I

An efficient method for the synthesis of substituted 4-quinolones via reaction of isatoic anhydride with ketone derived enolates and thencyclization of anthranilamides with polyphosphoric acid. The method provides anefficient and straightforward pathway for the synthesis of substituted 4-quinolones [134].



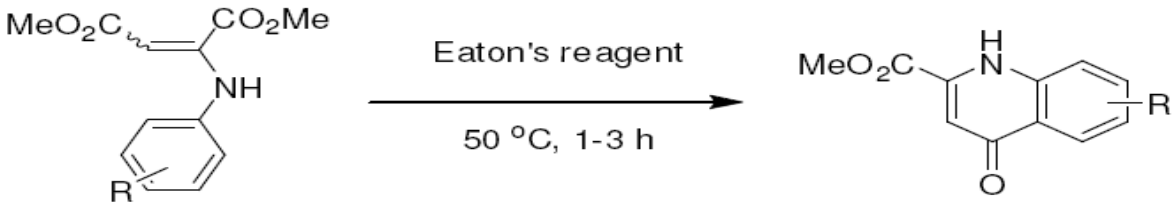
R= H, 4-CH_3, 4-Br, 4-Cl, 4-F 3-CH_3, 3-Br, 3-Cl, 2-CH_3

Synthesis of 4-quinolones by reaction of isatoic anhydride with triphenylphosphonium salts [135]. A nickel-catalyzed reaction of isatoic anhydride with alkynes to affrod 4-quinolones [136].



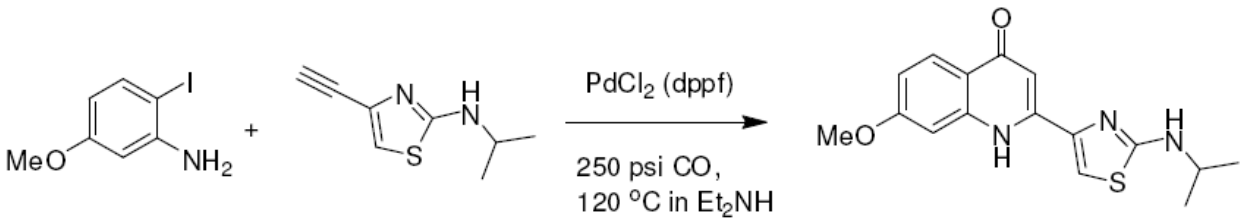
R_1= Ph, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, Me R_2= H, MeO R_3= H, CF_3

An efficient synthesis of 4-quinolones by cycloacylation of aniline derivatives in the presence of Eaton's reagent. This high yielding methodology is applicable to a wide variety of anilines and requires milder conditions than those traditionally employed and is characterized by relatively low reaction temprature and ease of product isolation [137].

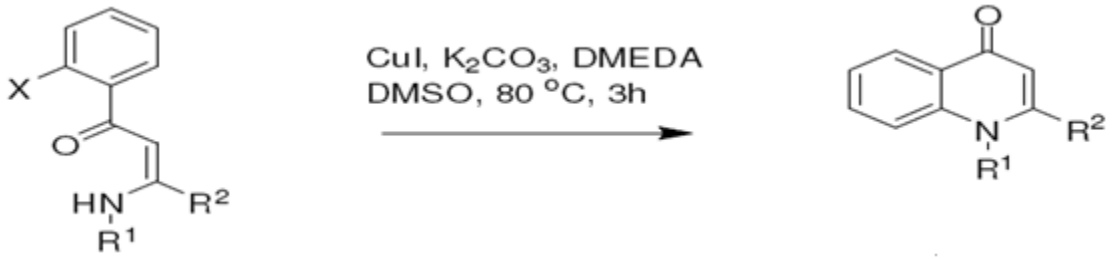


R= Cl, Br, OMe

Synthesis of 4-quinolone (key substructure of the protease inhibitor BILN 2061) via palladium-catalyzed carbonylative Sonoghasira coupling/cyclization of 2-iodomethoxyaniline with thiazolylacetylene [138].

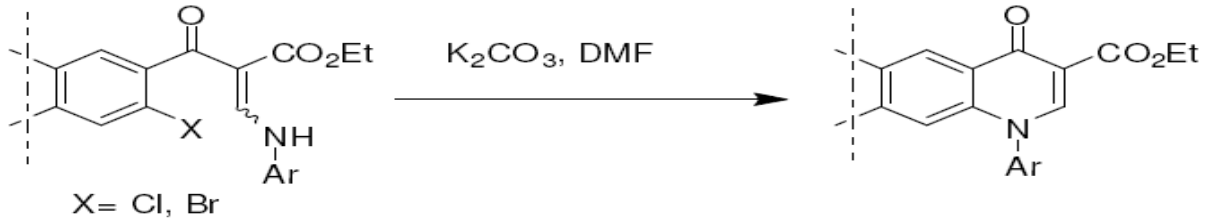


Synthesis of 4-quinolones via Cu-catalyzed cyclization of 1-(2-halophenyl)-2-en-3-amin-1-one. The reaction tolerates a variety of useful functionalities including ester, keto, cyano and chloro substituents [139].



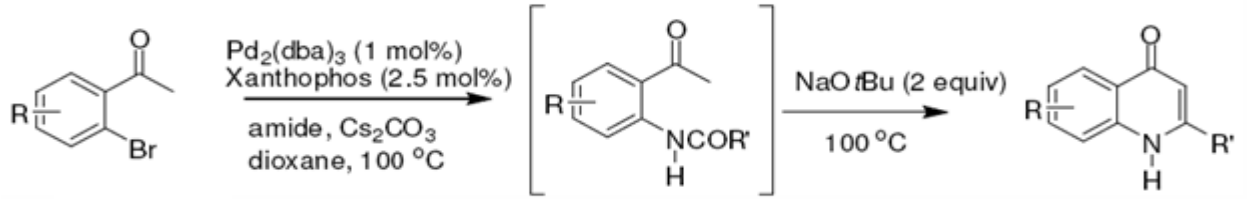
R_1= Ph, 4-$MeOC_6H_4$, 3-$CF_3C_6H_4$, *n*-Bu, *t* –Bu R_2= Ph, 4-ClC_6H_4, 3-$MeOC_6H_4$,4-AcC_6H_4

A base promoted cyclization of enamines for the synthesis of 4-quinolones [140].



X= Cl, Br

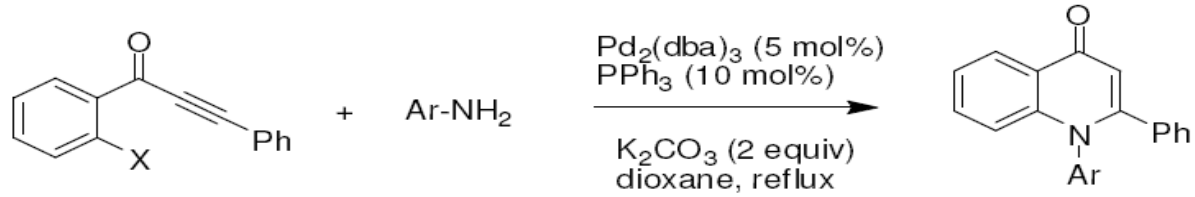
A mild, one pot synthesis of 4-quinolones via Pd-catalyzed amidation of 2-acetylbromoarenes and the subsequent base promoted cyclization. The easily available starting materials, mild reaction conditions, and simple manipulation makes this an attractive method for the synthesis of 4-quinolones [141].



R= H, 4-OMe

R'= alkyl, aryl

An efficient Pd-catalyzed tandem amination reaction for the synthesis of 4-quinolones in good to excellent yield from easily accessible ohaloaryl acetylenic ketones and primary amines [142].



X = Br, Cl

This has been noticed so far, that modifications on quinolinone moiety displayed valuable biological activities. It will be interesting to observe that these modifications can be utilized as potent therapeutic agents in future. The biological profiles of these new generations of quinolinone would represent a fruitful matrix for further development of better medicinal agents.

3.Conclusion:

From the above studies, the quinolinones compounds are an important group of bicyclic compounds. This has been noticed so far, that modifications on quinolinones moiety displayed valuable biological activities like anticonvulsant, antibiotic, antitubercular, antiallergic, antiproliferative, antiulcer, antihypertensive, anti-inflammatory, analgesic, antimicrobial, antioxidant, antihelmintics, and insecticidal activities etc. It will be interesting to observe that these modifications can be utilized as potent therapeutic agents in future. The synthesis of novel quinolinones derivatives remains a main focus of medicinal research. Since now, researchers have been attracted toward designing more potent benzimidazole derivatives having wide diverse of biological activity.

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