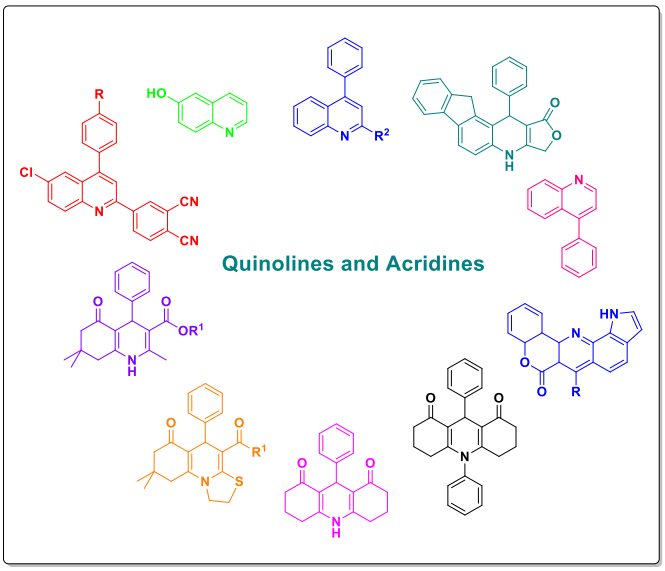
A brief overview on one pot multi-component synthesis and biological properties of a class of nitrogenous complex heterocyclic compounds



Abstract

The quinoline and acridine core possesses a vast number of biological activities such as anticancer, anti-malarial, anti-microbial, antifungal, anti-tubercular activities and the conventional classical synthetic methods have harsh conditions having multistep process. Currently scientists are searching new methodology to eliminate the use of chemicals, solvents and catalysts, which are hazardous to human health as well as to environment and so, this review provides a concise overview of new dimensions of one pot multi-component synthetic approaches in designing quinoline and acridine scaffold . This review would give more scientific ideas to synthesis a variety of heterocyclic moieties in a new synthetic way following the one-pot multi-component method.

Keywords: Quinolines, Acridines, 1,4-dihydropyridines, pyrido-pyrimidines, tetrazoloquinazolinones, One-pot reactions, Multicomponent synthesis

Introduction

Quinoline is a weak tertiary organic base and was discovered in 1834 as a colourless hygroscopic liquid by distillation of coal tar by Friedlieb Ferdiland Runge and in 1871, Dewar observed the chemical similarity between pyridine and quinoline having rigid heterocyclic core of benzene ortho-fused with a pyridine ring. (**Figure 1)** [1] Coal tar is a principal commercial source for quinoline synthesis but numerous reactions have been developed for its laboratory synthesis. Quinoline itself has a few applications but many of its derivatives are useful in various chemical reactions for laboratory synthesis. There are several reported classical synthetic routes for synthesising the quinoline structural motifs and such classical synthetic routes which are widely used include Skraup reaction, Conrad-Limpach reaction, Doebner reaction, Combes reaction, Povarov reaction, Doebner-Miller reaction, Gould Jacobs reaction and Riehm reaction. Which are majorly utilizes aniline as one of the common reactants (**Figure 2**). However, there are several other reactions such as Knorr reaction, Friedländer reaction, Pfitzinger reaction, Niementowski reaction, Meth-Cohn reaction and Camps reaction which requires special substituted anilines or other substituted reactants to yield quinoline structural motiffs.

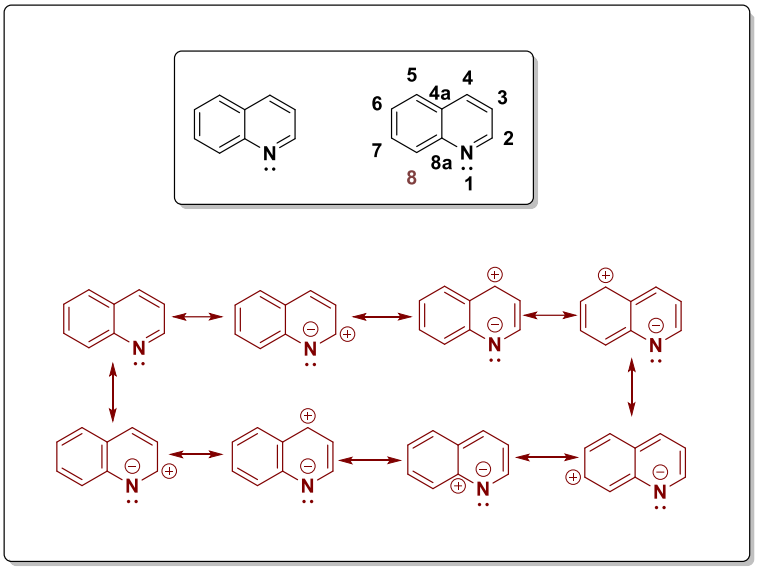


Figure 1 :Chemical structures and resonating structures of quinoline moiety

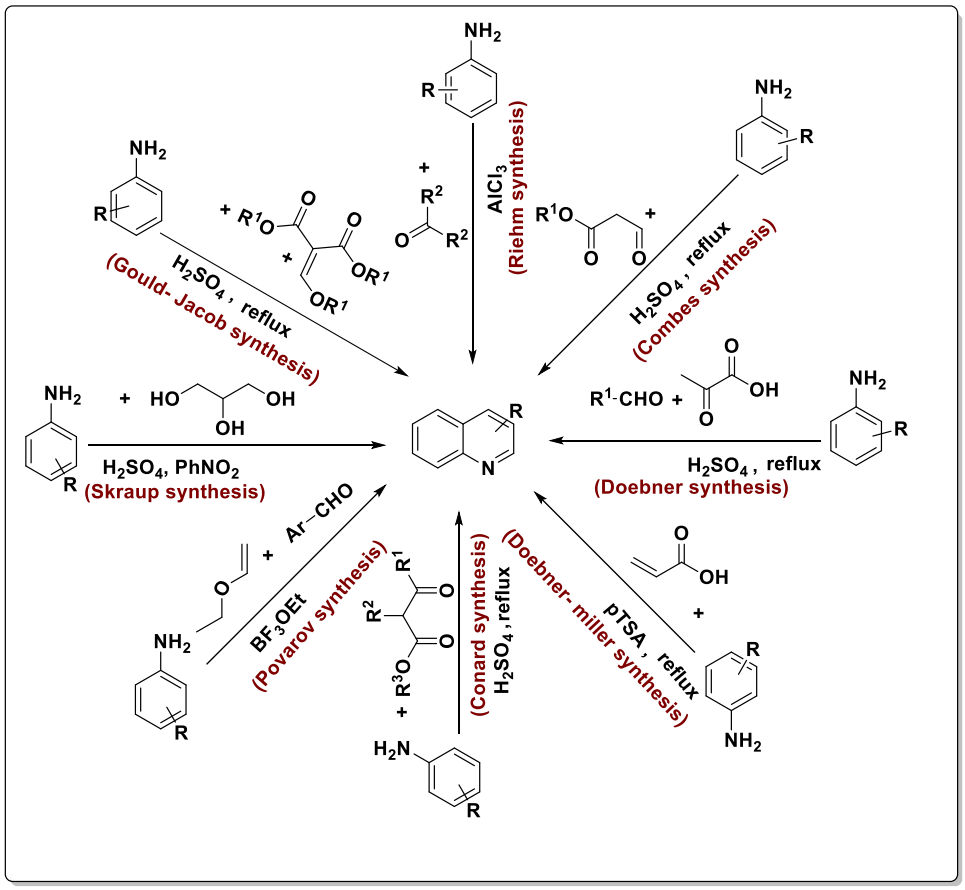


Figure 2: Diverse synthetic routes for the synthesis of quinoline structures

Quinoline scaffolds are well-known entity under alkaloid class of natural products and is present in various biologically active plants, pharmaceuticals, agrochemicals, dyes etc. and are represented in **(Figure 3)**.[2-3] They are also used as chelating agent due to multiple N-donor ligands and quinoline pharmacophore is a crucial functionality due to variety of pharmacological activities (**Figure 3**) such as anti-malarial, anti-protozoal, anti-tubercular, antibacterial, anticancer, anti-proliferative, antitumor, anti-inflammatory, antifungal, antioxidant, DNA binding, antihypertensive, anti-HIV agents. [4-12] High magnitude of pharmacological importance of natural or synthesized quinoline derivatives has urged various chemists world-wide to examine the utility and prominence of this scaffold by means of research reviews.

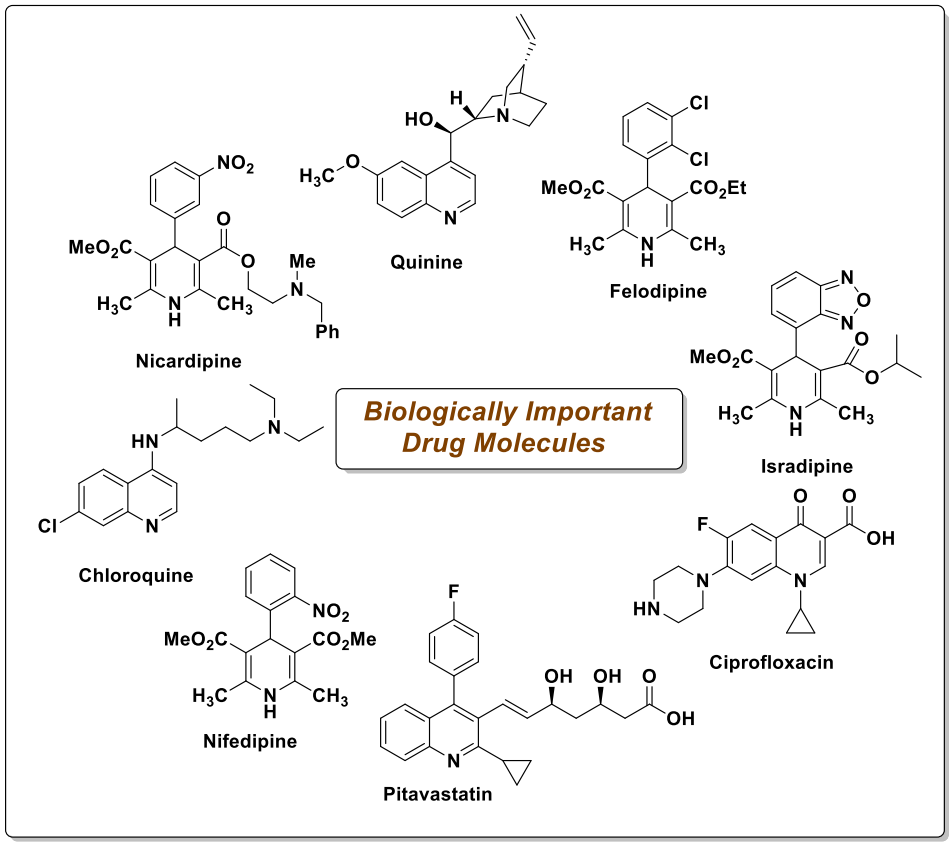


Figure 3: Some important pharmaceutically active drug molecule

Now, acridine is a nitrogeneous heterocyclic compound having planner shaped structural motif and it is also structurally closely resembles to anthacene with one of the central C-H group is replaced by 'N' atom. It is a basic organic compound due to the presence of Sp^2 -hybridised 'N' atom and the unsubstituted compound is generally colourless crystalline solid.[13] In 1870 Carl Grabe and Heinrich Caro first isolated acidine from coal tar by extracting with dil. H_2SO_4 .[14] Acrinines have broad range of research and industrial applications in various fields such as in medicinal chemistry, fluorescent organic dye, chemosensor, photo catalysis, as hole transport materials in solar cell and photovoltaic applications.[15-23] Acridinium ions are used as efficient organic photo catalyst for many organic transformations due to their long excited state lifetime and tunable redox potential.[24-25] There are various procedures [26-35] for the synthesis of acridine structural motifs but at the very first Bernthsen et. al have synthesized it in laboratory by using diphenylamine and carboxylic acid in presence of anhydrous $ZnCl_2$. [36]. There are also other methods (**Figure 4**) which have been developed in recent years and which has opened a broad window for the organic synthesis of acridine structural motifs.

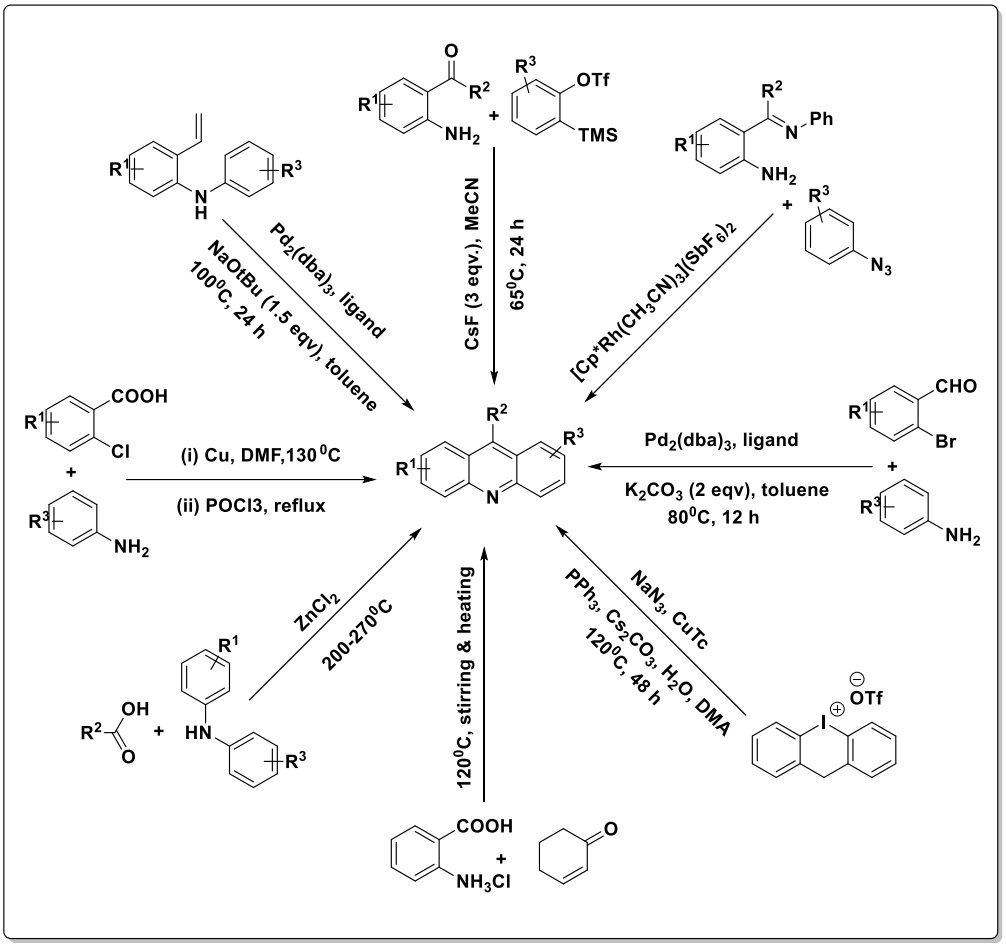


Figure 4: Diverse synthetic routes for the synthesis of acridine structures

Acridine derivatives have been used for the preparation of labeled medicinal conjugates such as nucleic acids, peptides, and proteins that exhibit antitumor and DNA-binding properties [37-39]. Among other acridine derivatives, substituted 1,8-Dioxo-decahydroacridines and their derivatives have been widely used in medicinal chemisty as can behave as alternative of 1,4-dihydropyridines from a variety of viewpoints such as biological activities and due to close resemblance with 1,4-dihydropyridines in respect of the biological properties 1,8-Dioxo-decahydroacridines have been use as calcium channel blockers for the treatment of defibrillation and hypertension disease [40-42]. They also

possesses antimalarial, antiviral, antibacterial, antiallergic and anicancer properties and recently, acridines showed some inhibition properties for multidrug resistance in tumour cell lines and some of the acridine drugs are exhibiting promising anticancer activity both in vitro and in vivo against a range of murine and human cancers cells.[43-46] And additionally due to having fluorescent properties they are being used as molecular probes for monitoring polymerization processes in biological cells.[47]

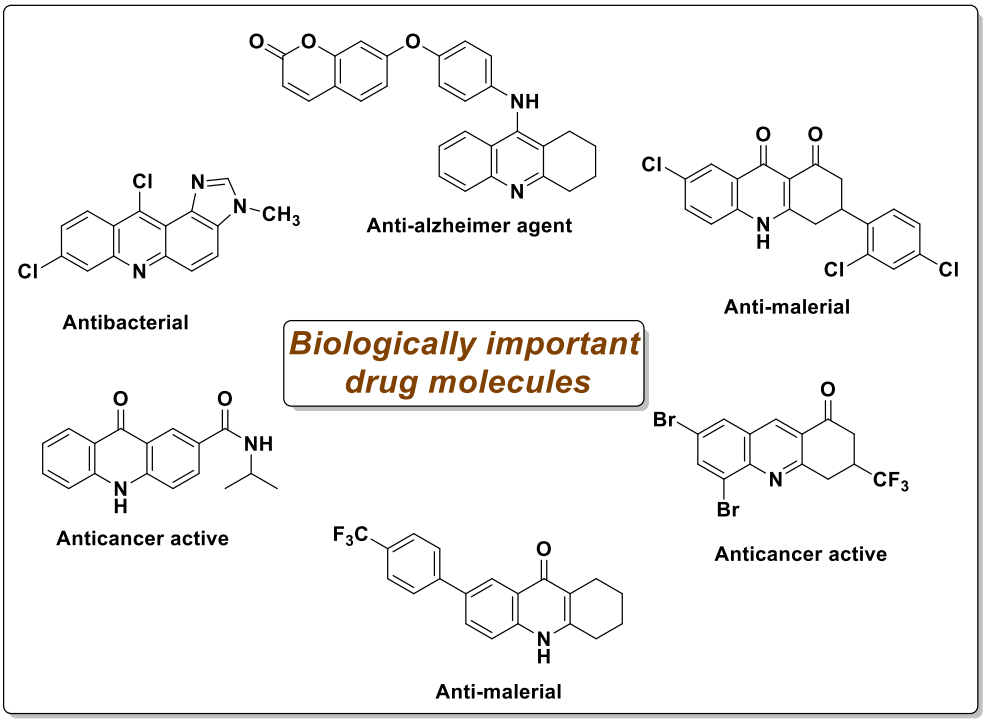
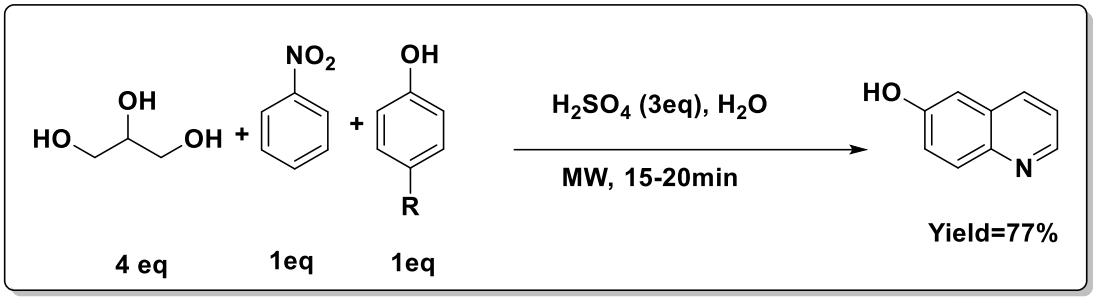


Figure 5: Some important pharmaceutically active drug molecule

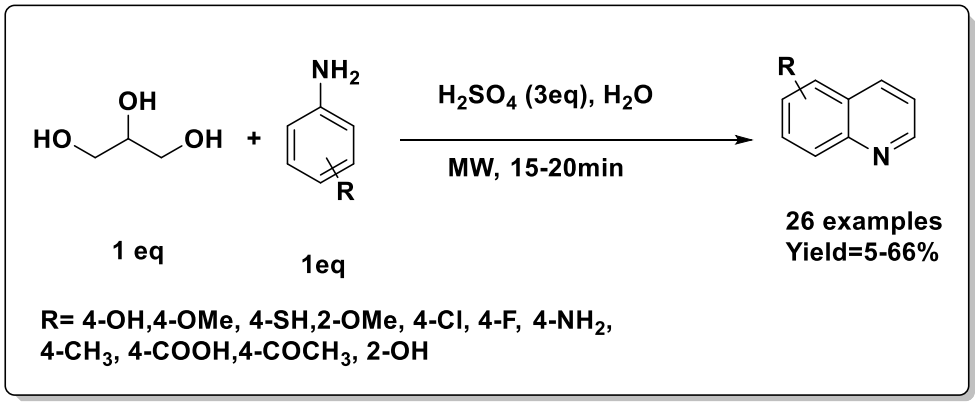
Methods of synthesis of quinoline derivatives

In 2014, Saggadi. *et al*. had developed a synthetic method following Skraup reaction and Bamberger rearrangement reaction in water using glycerol, nitrobenzene and *p*-aminophenol or *p*-nitrophenol as reactants. The process involved the presence of sulphuric acid under microwave irradiation condition (**Scheme 1**) with yield upto 77%..[48]



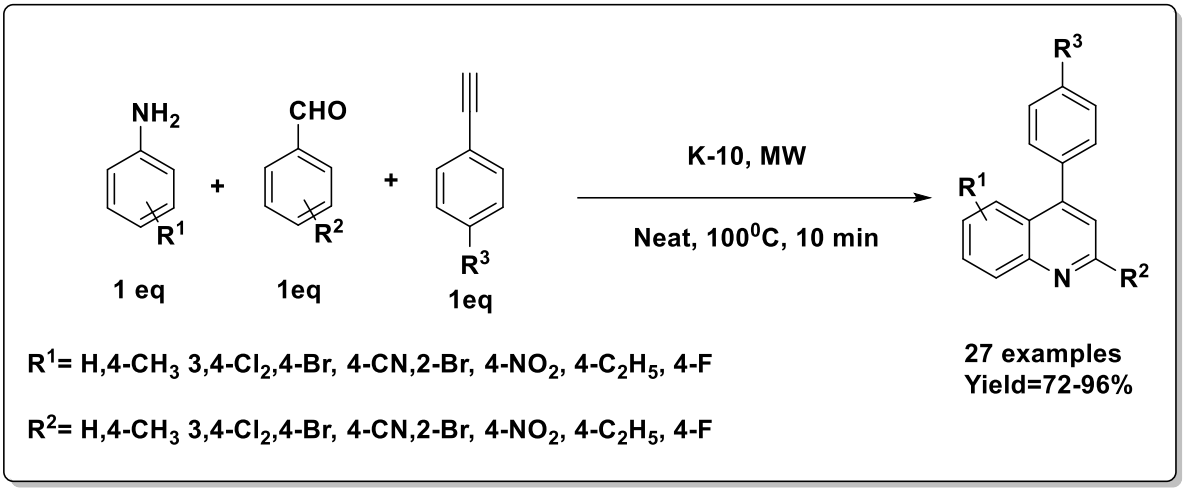
Scheme 1: Microwave assisted regioselective modified Skraup reaction and Bamberger rearrangment reported by Saggadi.*et al.*

In 2014, Saggadi. *et al*. had developed a synthetic method following Skraup reaction and Bamberger rearrangement reaction in water using glycerol, nitrobenzene and *p*-aminophenol or *p*-nitrophenol as reactants. The process involved the presence of sulphuric acid under microwave irradiation condition (**Scheme 2**) with yield upto 66%.[49]



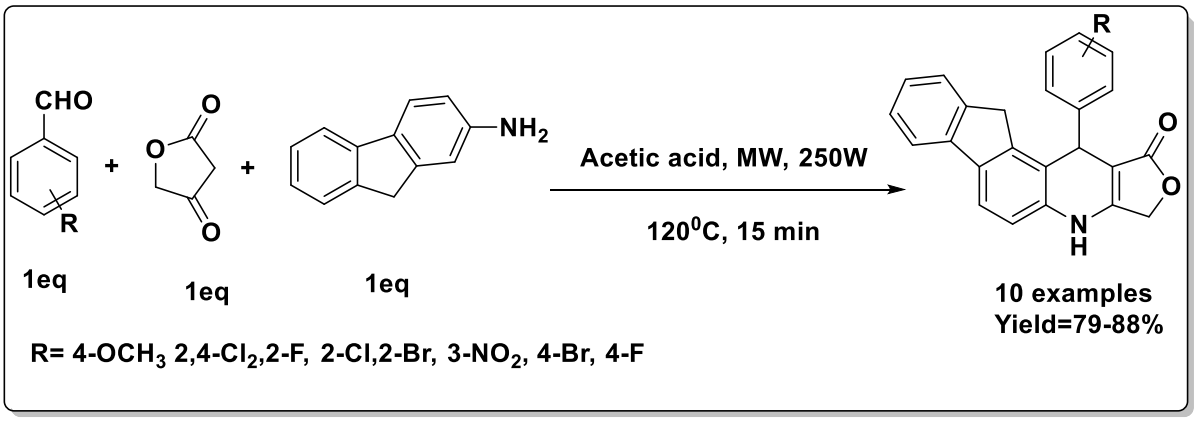
Scheme 2: Green Skraup protocol under microwave irritation reported by Saggadi.*et al*.

In 2010, Tork.*et al*. had developed a synthetic method for the synthesis of quinoline derivatives using aniline derivatives, aldehydes and aromatic alkynes as reactants as reactants under microwave condition. The process involved the presence of K-10, neat condition and 100^0C temperature (**Scheme 3**) with yield upto 96%.[50]



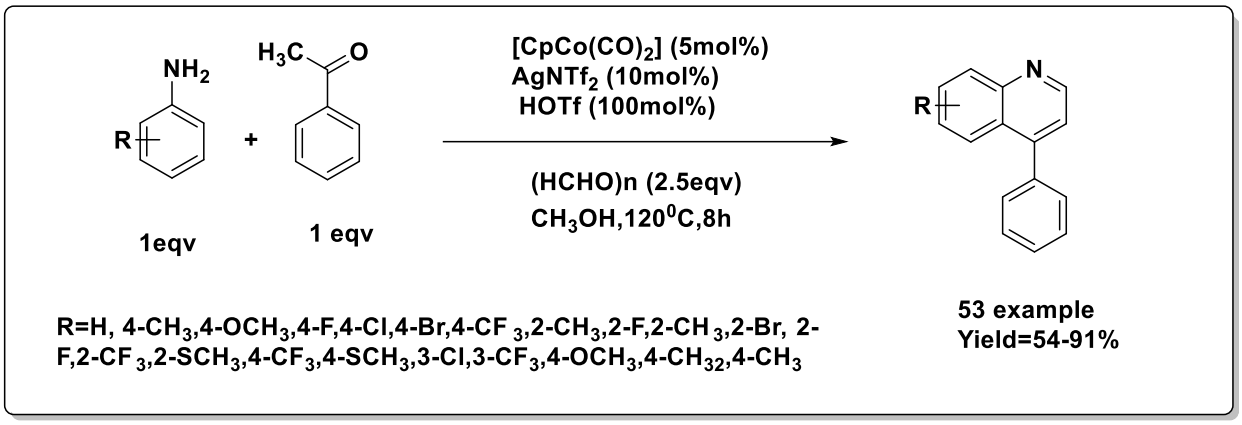
Scheme 3 : Microwave assisted solvent free protocol reported by Kulkarni and Tork.*et al.*

In 2013, Peng.*et al*. had developed a synthetic method for the synthesis of quinoline derivatives using aniline derivatives using aldehydes, aromatic amine, cyclic 1,3-diketo esteras as reactants. The process involved the presence of acetic acid under microwave irradiation condition (**Scheme 4**) with yield upto 88%.[51]



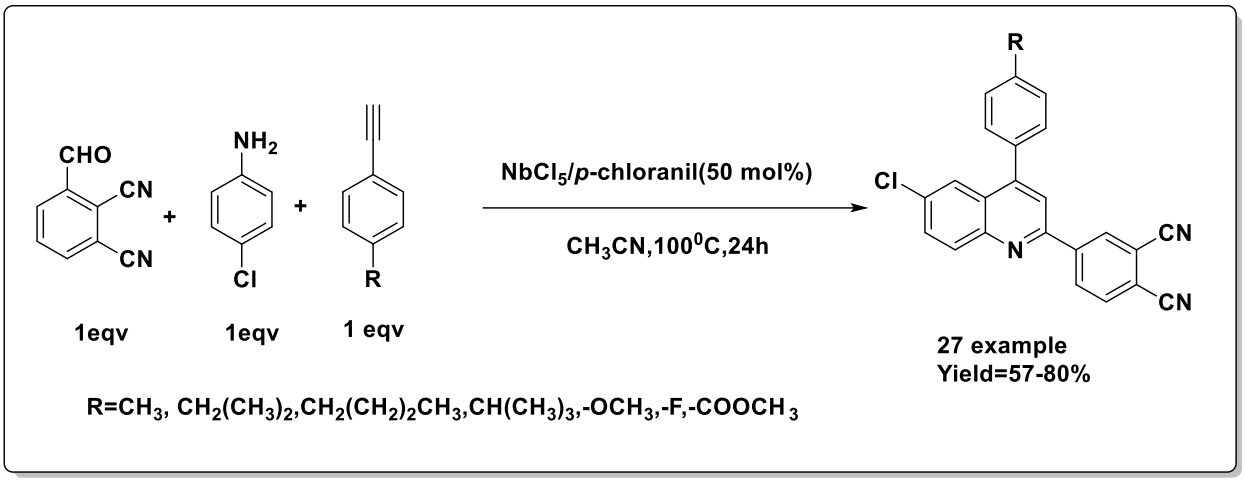
Scheme 4: Microwave influenced solvent free protocol reported by Peng.*et al*.

In 2017, Xu *et al*. had developed a synthetic method for the synthesis of quinoline derivatives using aniline derivatives using aldehyde, aromatic amines as reactants. The process involved the presence of PEG and methanol at 120^{0}C temperature (**Scheme 5**) with yield upto 91%.[52]



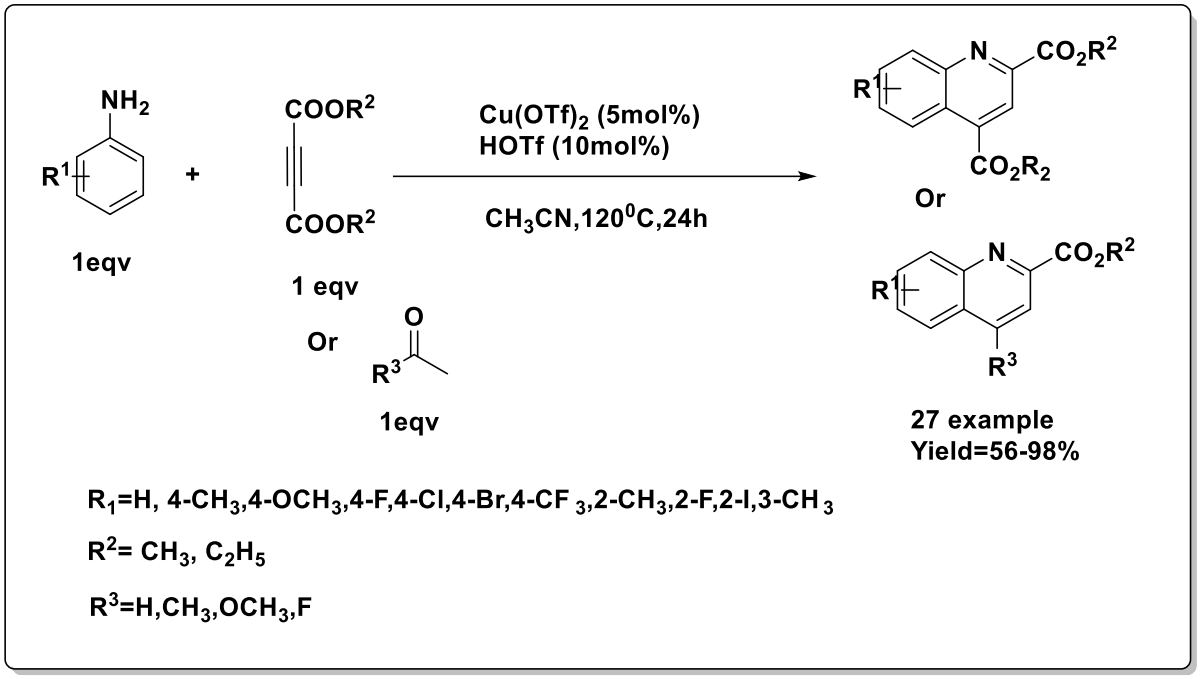
Scheme 5: Cobalt (III) based catalyst for quinolone synthesis reported by Xu et al.

In 2018, Aloisio. *et al*. had developed a synthetic method for the synthesis of quinoline derivatives using aniline derivatives using aromatic primary amines, cyano-aldehyde, aromatic alkyne and as reactants. The process involved the presence of $NbCl_5$ /*p*-chloranil in presence of CH_3CN as solvent under 100^0C temperature.(**Scheme 6**) with yield upto 77%.[53]



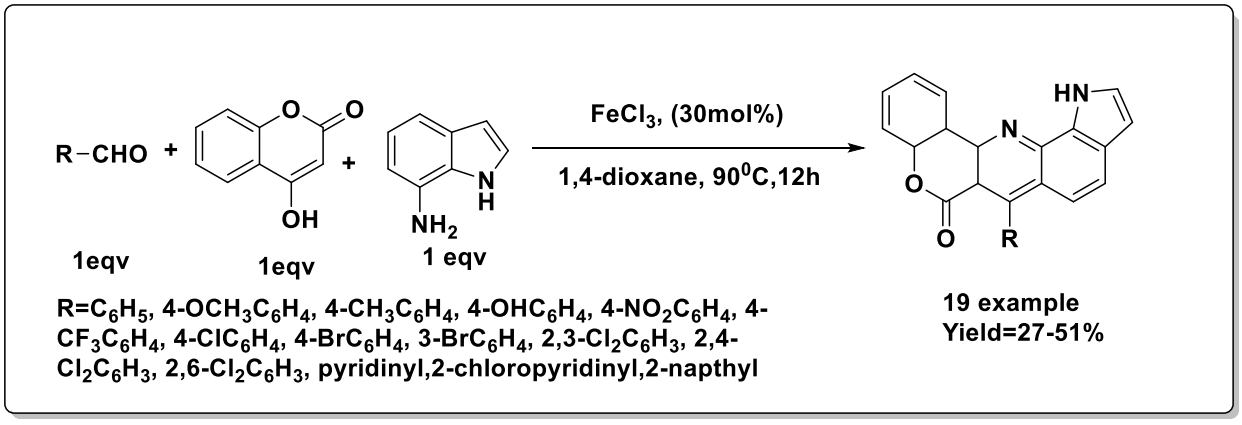
Scheme 6: Multicomponent reaction reported by Aloisio.*et al.*

In 2018, Wu.*et al*. had developed a synthetic method for the synthesis of quinoline derivatives using aromatic amine, alkynes and ketones as reactants. The process involved the presence of $Cu(OTf)_2$, HOTf as catalyst and CH_3CN as solvent under 120^0C.[54]



Scheme 7: Regioselective copper catalyzed protocol reported by Wu.*et al.*

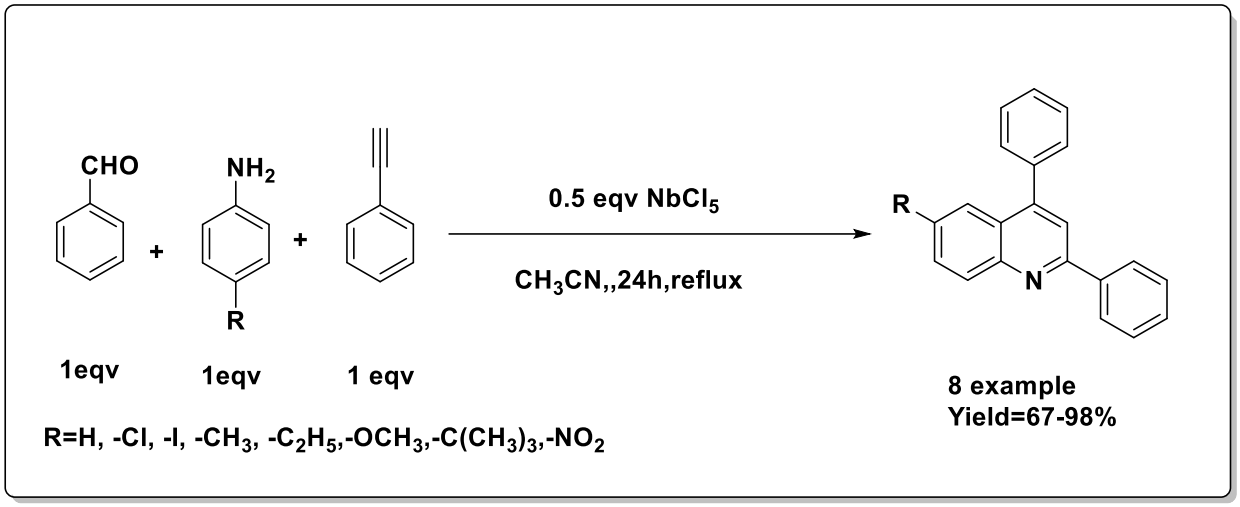
In 2017, Thigulla. *et al*. had developed a synthetic method for the synthesis of quinoline derivatives using aniline derivatives using aldehyde, 4-hydroxycoumarine and 6-aminoindole as reactants. The process involved the presence $FeCl_3$ as catalyst in 1,4-dioxane solvent under thermal condition (**Scheme 8**) with yield upto 51%.[55]



Scheme 8: $FeCl_3$ catalyzed synthesis of quinolone reported by Thigulla.*et al*.

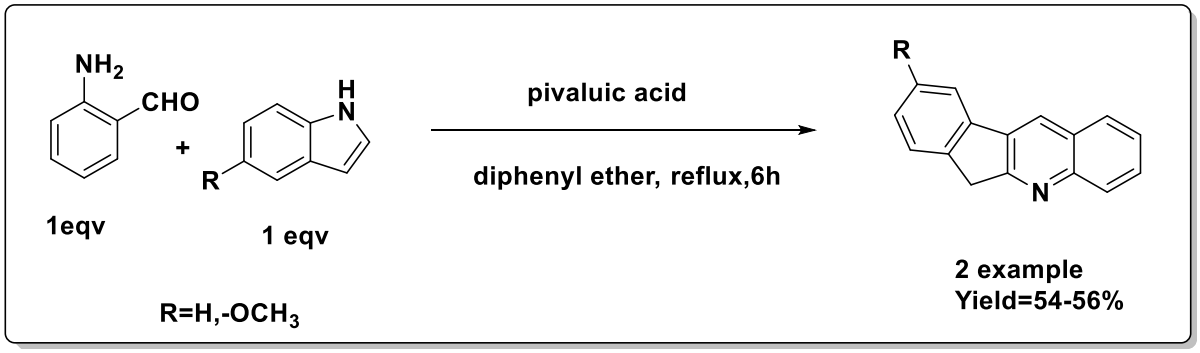
In 2015, Andrade.et al. had developed a synthetic method for the synthesis of quinoline derivatives using aniline derivatives, aldehyde and alkyne as reactants. The process involved the

presence $NbCl_5$ as catalyst under thermal condition in CH_3CN solvent (**Scheme 9**) with yield upto 98%.[56]



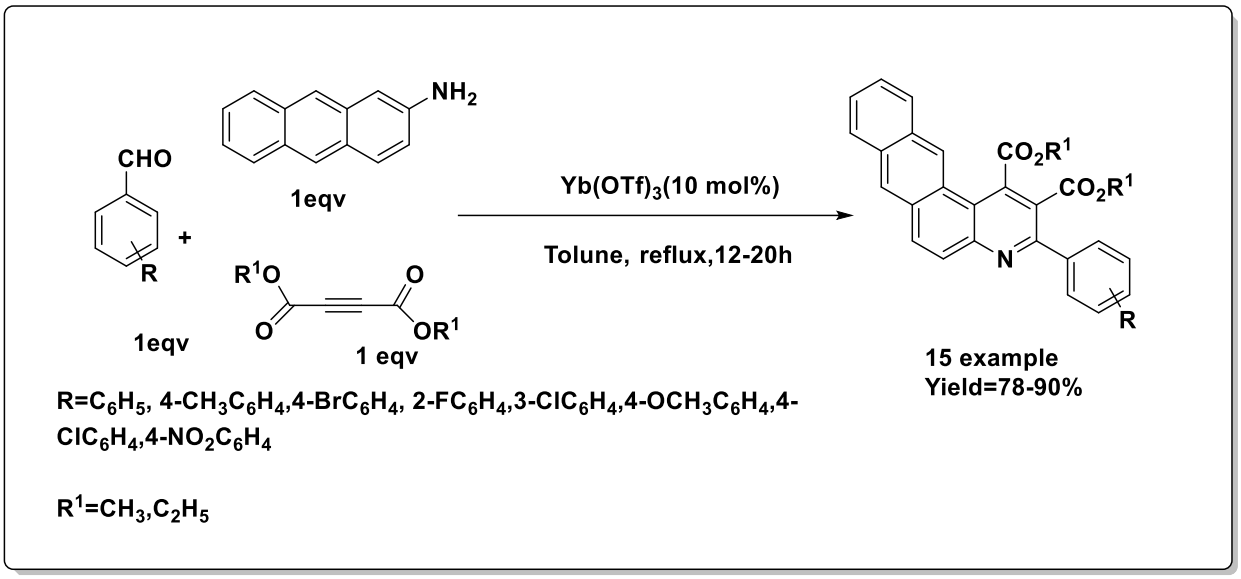
Scheme 9: Niobium pentachloride as catalyst for qunoline synthesis reported by Andrade.*et al.*

In 2016, Tilve.*et al*. had developed a synthetic method for the synthesis of quinoline derivatives using 2-aminobenzaldehyde and indole derivatives as reactants. The process involved the presence of pivaluic acid under reflux condition (**Scheme 10**) with yield upto 56%.[57]



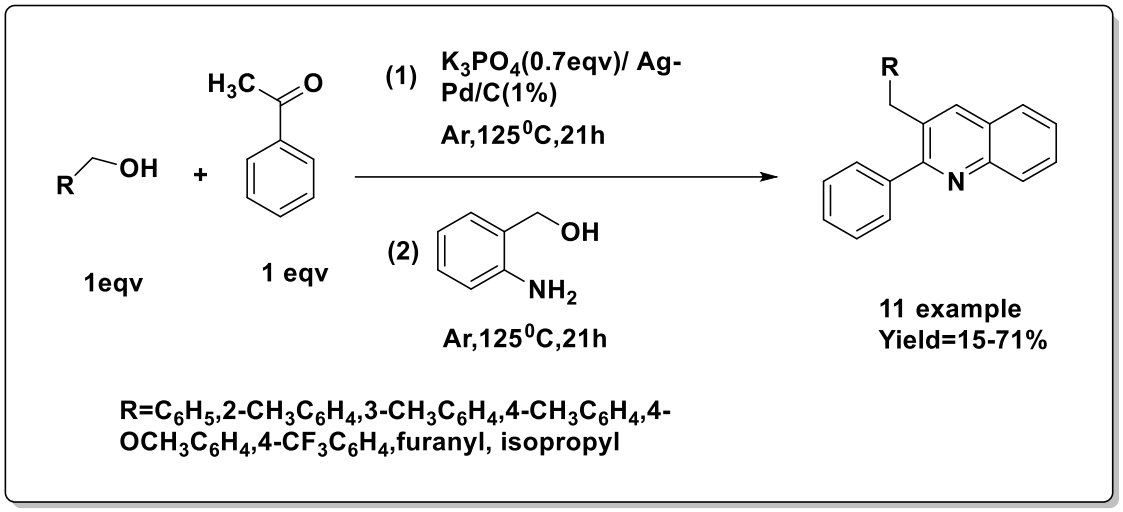
Scheme 10: Pivalic acid catalyzed synthesis reported by Kadam and Tilve.*et al*.

In 2014, Zhaou.*et al*. had developed a synthetic method for the synthesis of quinoline derivatives using aldehydes, aromatic primary amines and alkyne diester derivatives as reactants. The process involved the presence of $Yb(OTf)_3$ in tolune under reflux condition (**Scheme 11**) with yield upto 90%.[58]



Scheme 11: Ytterbium triflate [$Yb(OTf)_3$] catalysed synthesis reported by Zhou *et al.*

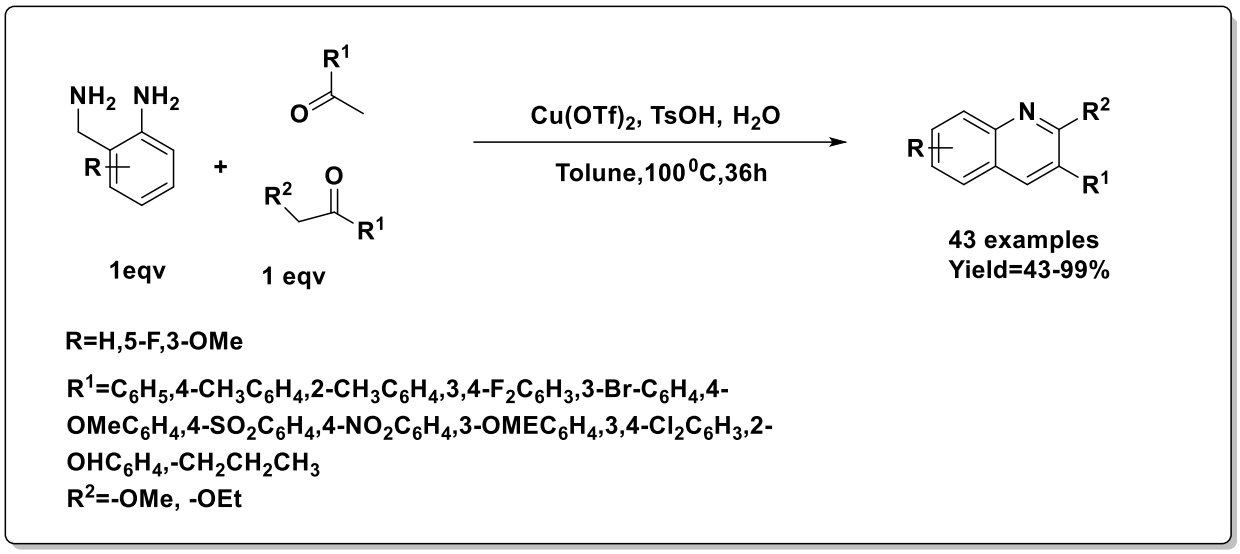
In 2013, Chen.*et al*. had developed a synthetic method for the synthesis of quinoline derivatives using benzaldehyde ,alcohols and primary aromatic aminoalcohol derivatives as reactants. The process involved the presence of K_3PO_4/ Ag-Pd-C as catalyst under reflux condition (**Scheme 12**) with yield upto 71%.[59]



Scheme 12: Synthesis of quinolines reported by Chen.*et al*

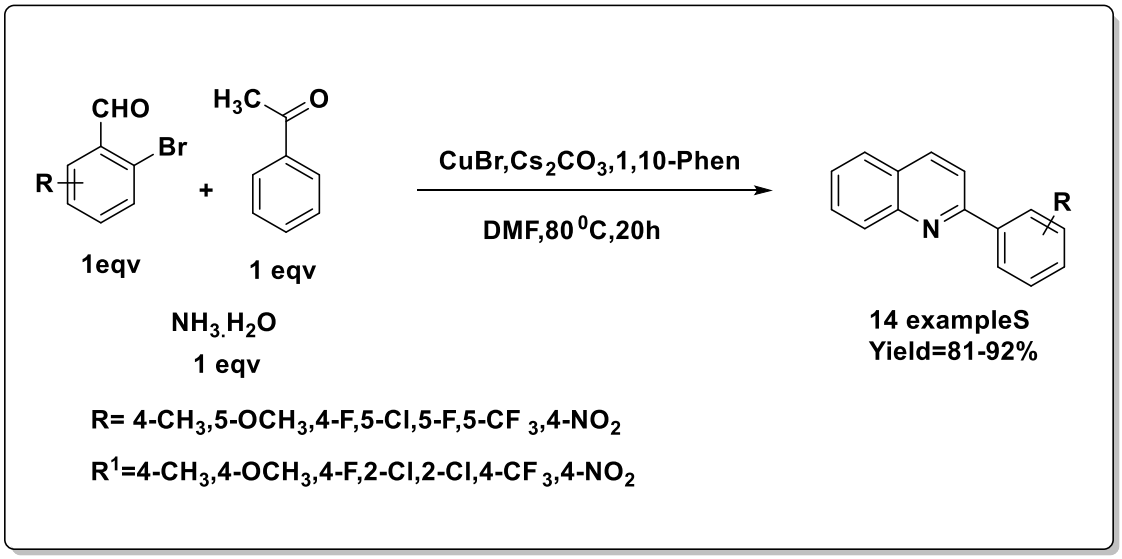
In 2015, Long-Yi.*et al*. had developed a synthetic method for the synthesis of quinoline derivatives using ketones and amine derivatives as reactants. The process involved the presence

of $Cu(OTf)_2$,TsOH, H_2O as catalyst in toluene under heating condition (**Scheme 13**) with yield upto 99%.[60]



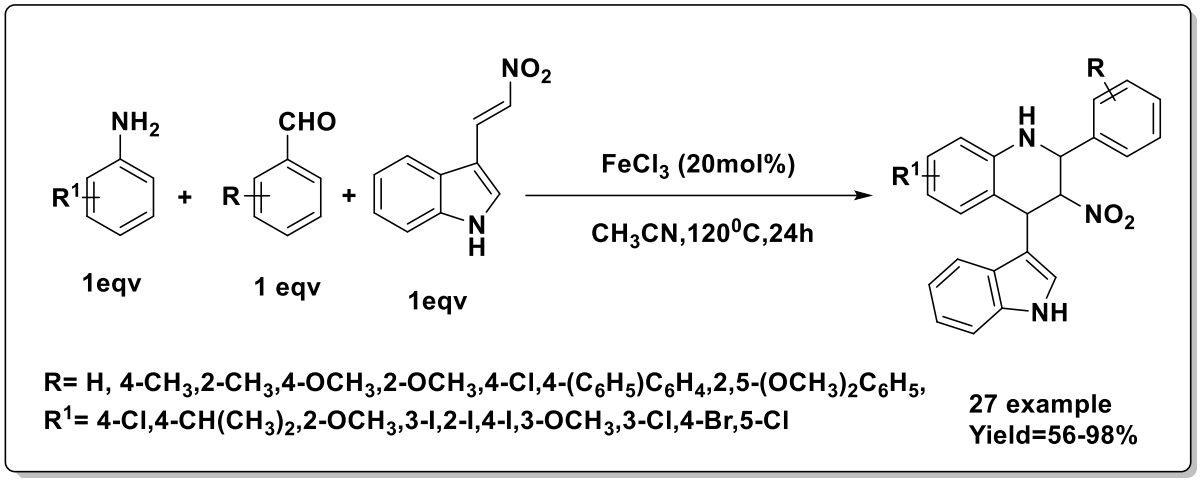
Scheme 13: Copper catalyzed C-N cleavage reported by Long-Yi.*et al*.

In 2014, Li.*et al*. had developed a synthetic method for the synthesis of quinoline derivatives using o-bromobenzaldehyde derivatives, acetophenone and ammonia as reactants. The process involved the presence of CuBr, Cs_2CO_3 as catalyst in DMF under heating condition (**Scheme 14**) with yield upto 92%.[61]



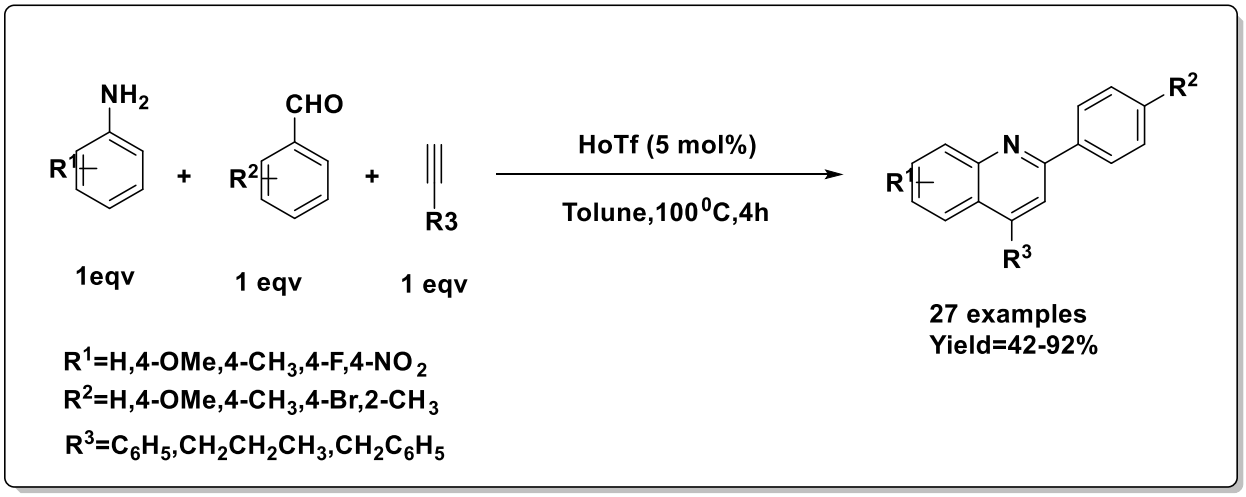
Scheme 14: Copper catalyzed reaction protocol reported by Li.*et al*.

In 2014, Zanwar.*et al* had developed a synthetic method for the synthesis of quinoline derivatives using primary aromatic amines, aldehydes and indole derivative as reactants. The process involved the presence of $FeCl_3$ as catalyst in CH_3CN under heating condition (**Scheme 15**) with yield upto 98%.[62]



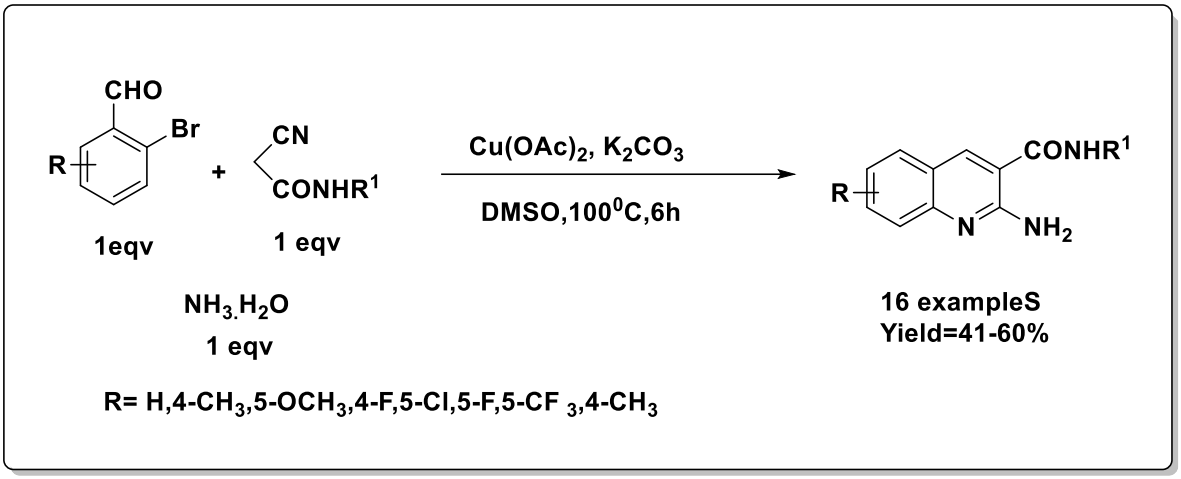
Scheme 15 : Mild reaction protocol reported by Zanwar.*et al*.

In 2014, Zhang.*et al*. had developed a synthetic method for the synthesis of quinoline derivatives using primary aromatic amines, aldehydes and alkyne derivative as reactants. The process involved the presence of HoTf as catalyst in toluene under heating condition (**Scheme 16**) with yield upto 92%.[63]



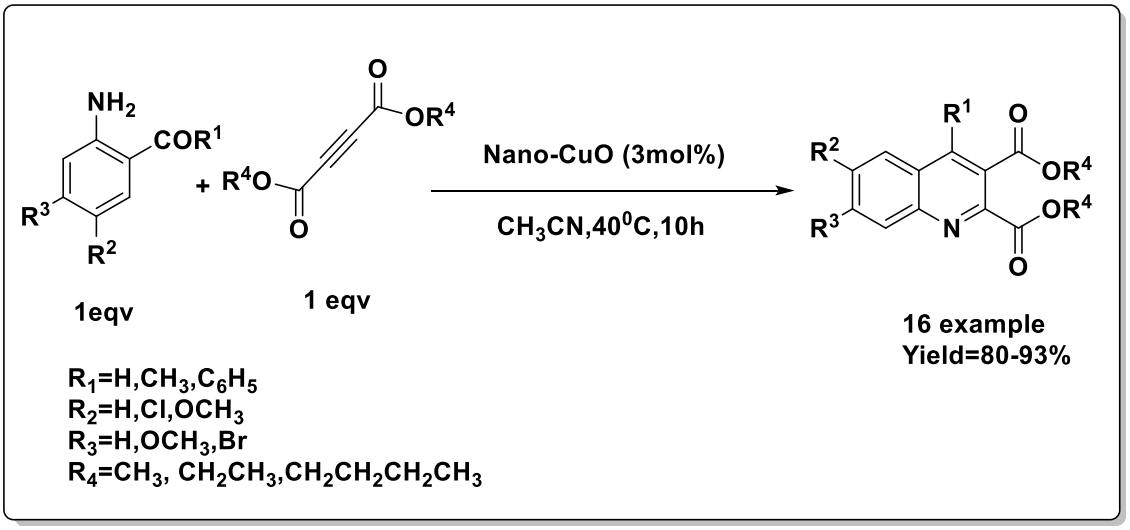
Scheme 16: Mild reaction protocol reported by Zhang *et al*.

In 2015, Zhang.*et al*. had developed a synthetic method for the synthesis of quinoline derivatives using o-bromobenzaldehydes derivatives, active methyline compound and ammonia as reactants. The process involved the presence of $Cu(OAc)_2$, K_2CO_3 as catalyst in DMSO under heating condition (**Scheme 17**) with yield upto 60%.[64]



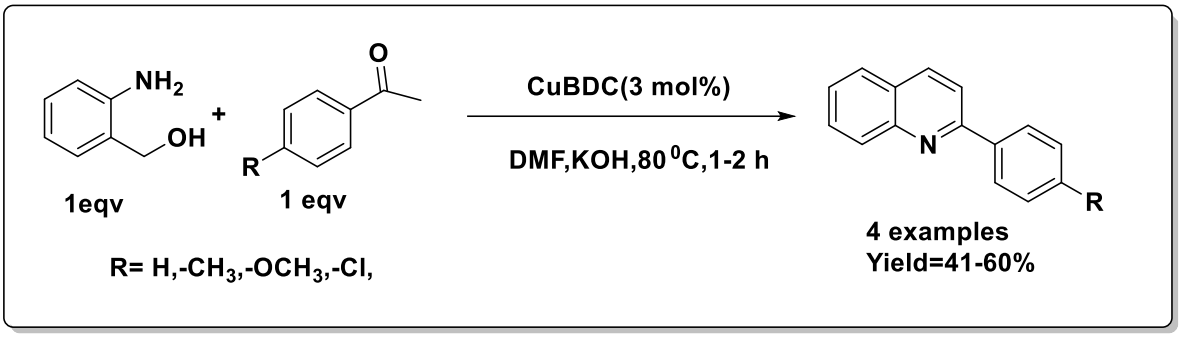
Scheme 17: Mild reaction protocol reported by Zhang *et al*.

In 2012, Venkanna.*et al*. had developed a synthetic method for the synthesis of quinoline derivatives using primary aromatic-ketone derivative, and alkyne diester derivatives as reactants. The process involved the presence of Nano-CuO as catalyst in CH_3CN under heating condition (**Scheme 18**) with yield upto 93%.[65]



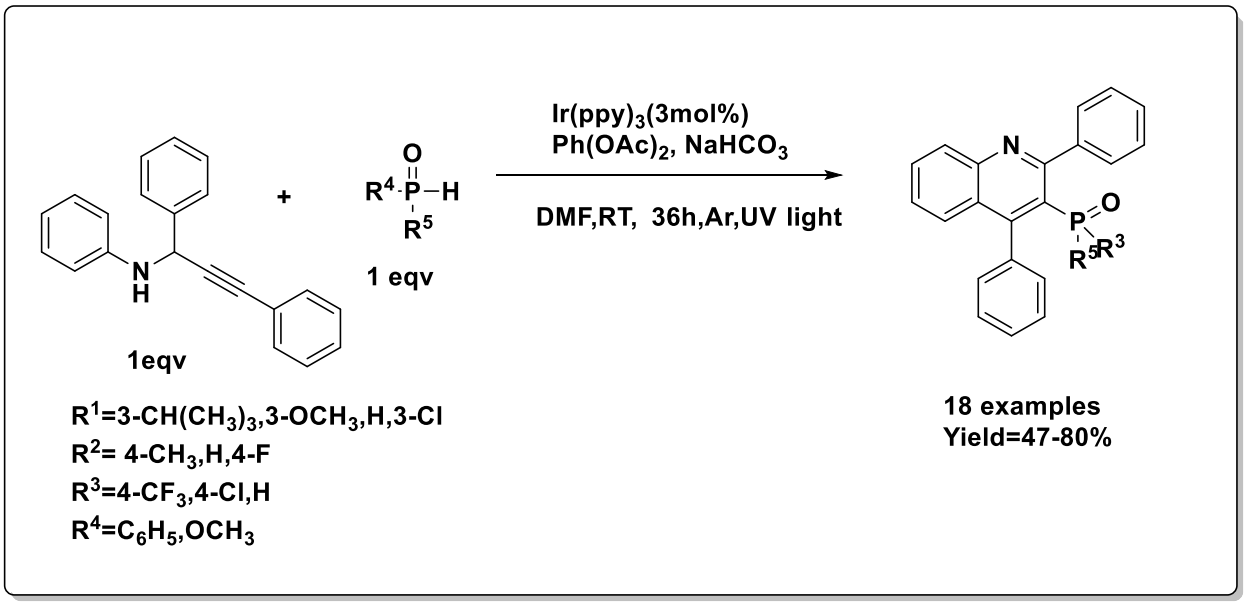
Scheme 18: Mild reaction protocol reported by Venkanna *et al*.

In 2013, Phan.*et al*. had developed a synthetic method for the synthesis of quinoline derivatives using primary aromatic aminoalcohol, aromatic ketone derivative as reactants. The process involved the presence of CuBDC as catalyst in alkaline DMF under heating condition (**Scheme 19**) with yield upto 60%.[66]



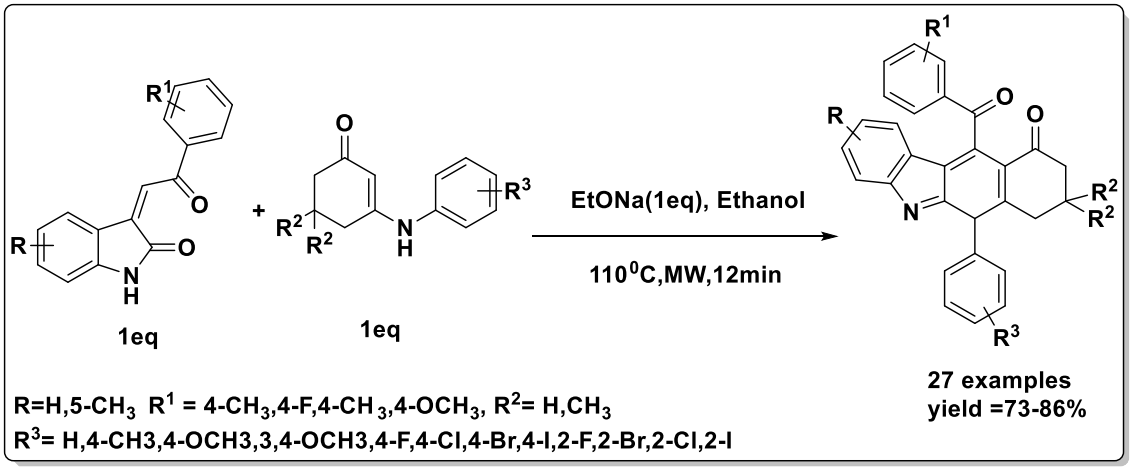
Scheme 19: Cu catalysed reaction reported by Phan *et al.*

In 2015, Shushizadeh.*et al*. had developed a synthetic method for the synthesis of quinoline derivatives using primary aromatic aminoalkine derivatives, dialkyle phosphate derivatives as reactants. The process involved the presence of $Ir(ppy)_3$, $Ph(OAc)_2$, $NaHCO_3$as catalyst in DMF under room temperature condition with UV light (**Scheme 20**) with yield upto 80%.[67]



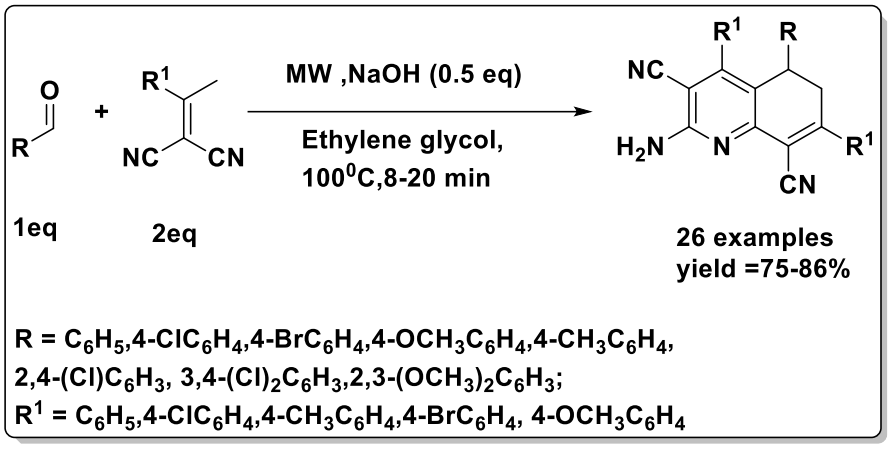
Scheme 20 : Iridium catalysed reaction reported by Shushizadeh *et al.*

In 2014, Li *et al*. developed a protocol to synthesize biologically active quinolines using 3-aroylidene-2-oxindoles with enaminones in presence of sodium ethoxide (NaOEt) in ethanol at 110°C under microwave condition with 27 examples having yield 73% to 86% (**Scheme 21**). [68]



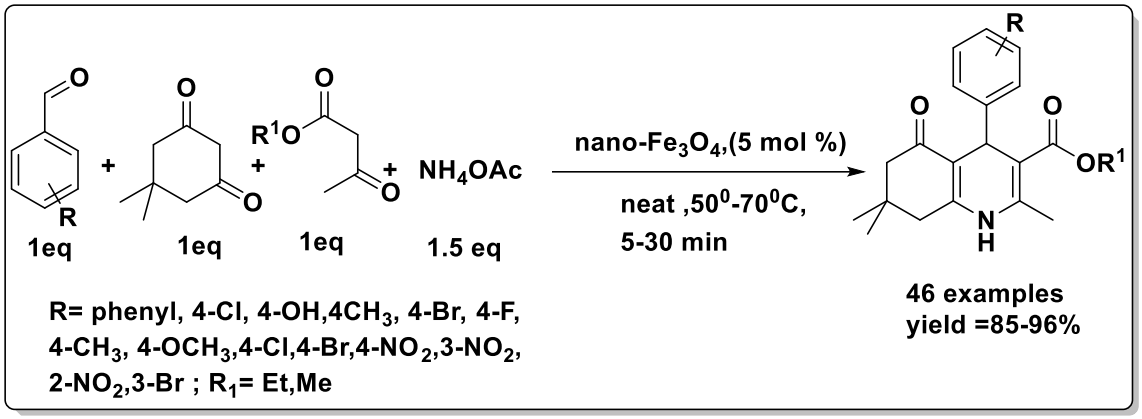
Scheme 21: Base promoted (3+3) Cycloaddition reaction under microwave reported by Li *et al*.

In 2012, Yu.*et al*. designed a three component synthesis of polysubstituted dihydroquinoline from aromatic aldehydes and 1-arylethylidenemalononitrile in presence of sodium hydroxide as base in ethylene glycol under microwave irradiation having 26 examples with yield from 75% to 86 % (**Scheme 22**). [69]



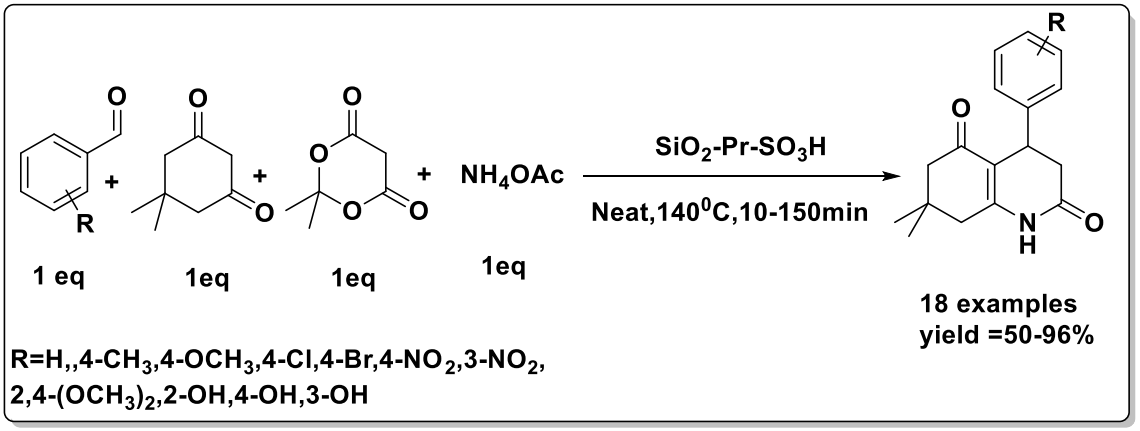
Scheme 22: Base catalyzed Domino reaction under microwave reported by Yu.*et al*.

In 2014, Esfahani.*et al*. and Khazaei *et al*. performed iron (III) oxide nanoparticles catalyzed synthesis of polyhydroquinolines under solvent free conditions using aromatic, cyclic and heterocyclic aldehydes, dimedone, βketoesters and ammonium acetate at 50°C under solvent free conditions (**Scheme 23**) having 46 examples with yield upto 96% [70-71]



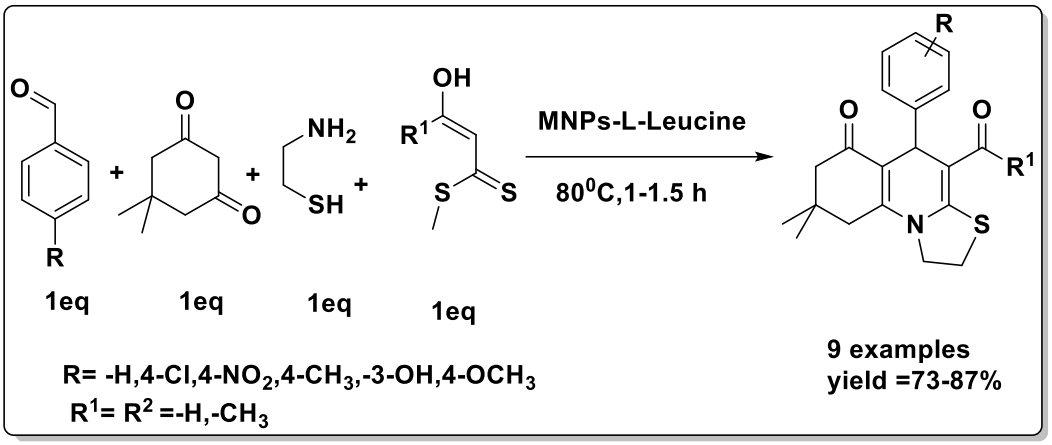
Scheme 23: Solvent free reaction reported by Esfahani.*et al.*

In 2015, Ziarani.*et al* synthesized dioxo-octahydroquinolines in one pot method using aromatic aldehydes , dimedone , Meldrum's acid and ammonium acetate and sulfonic acid functionalized SiO_2-Pr-SO_3H as catalyst under solvent-free condition.(**Scheme 24**).[72] The procedure has some greener advantages having 18 examples with yield up to 96%.



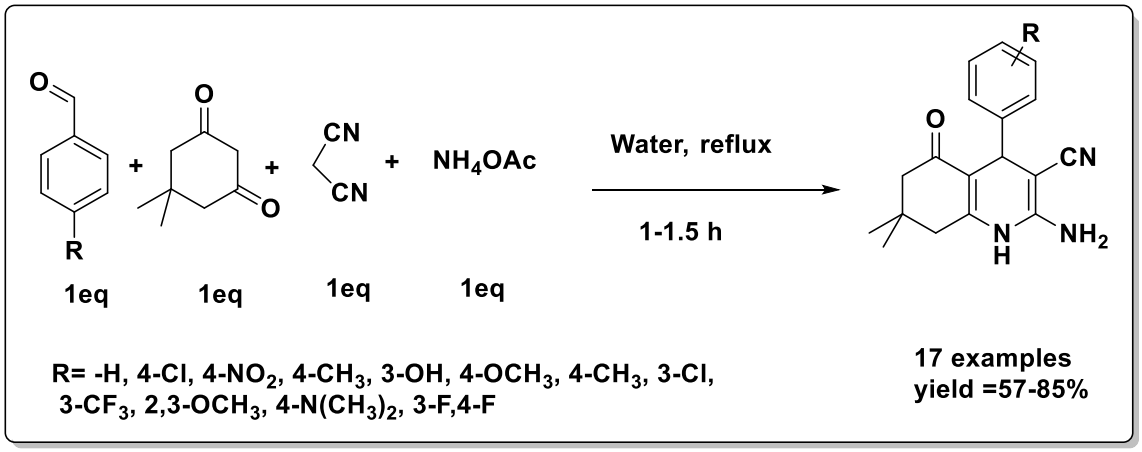
Scheme 24: Microwave assisted silica based catalyst reported for octahydroquinolines by Ziarani.*et al.*

In 2016, Arabpoor.*et al.* synthesized synthesis of thiazoloquinolines using superparamagnetic silica-encapsulated ϒ-Fe_2O_3 supported L-Leucine nanoparticles by the four-component reaction of α-enolicdithioesters , cysteamine , aromatic aldehydes and dimedone under thermal solvent-free condition at 80°C in one hour having 9 examples with yield between 73-93% yield (**Scheme 25**) [73]



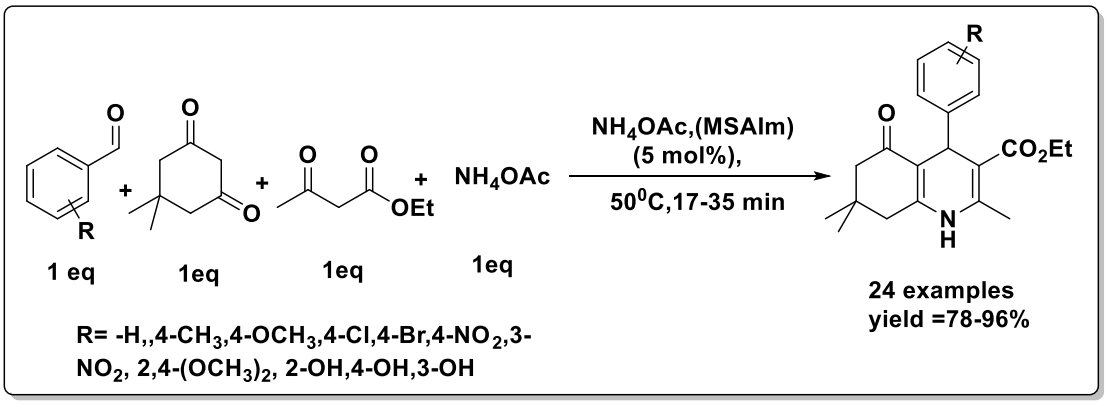
Scheme 25: Biocatalyst based reaction protocol reported by Arabpoor and Shaterian *et al.*

In 2017, Patil.*et al.* had done a catalyst-free method for the synthesis of hexahydroquinolinones in single pot four component method taking dimedone, ammonium acetate, aryl aldehydes and malanonitrile as substrate in water having 17 examples with yield between 57-85% yield (**Scheme 26**) [74]



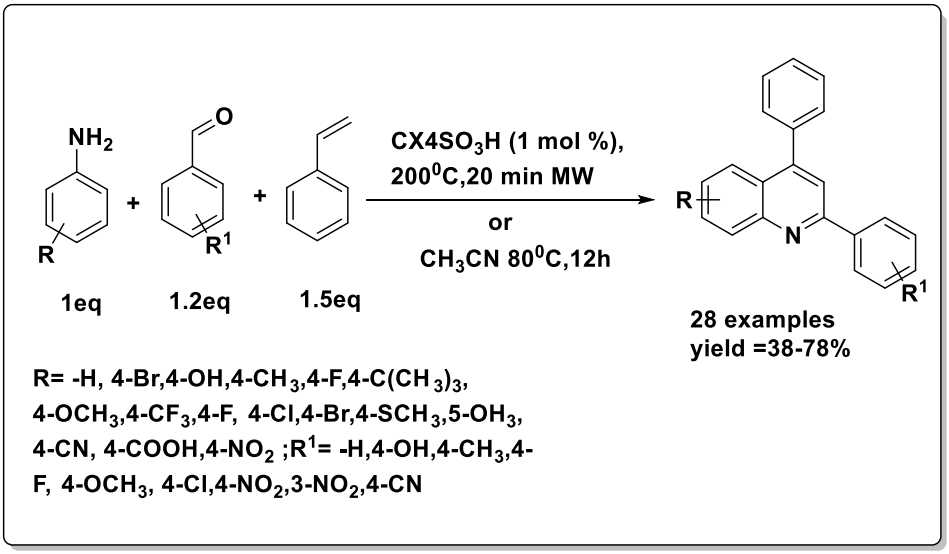
Scheme 26: Catalyst free synthesis protocol reported by Patil.*et al.*

In 2014, Khaligh.*et al*. had done a four-component one-pot synthesis of synthesis of unsymmetrical polyhydroquinoline derivatives from aryl/heteroaryl aldehydes, ethyl acetoacetate , dimedone and ammonium acetate under solvent-free conditions at 50°C. having 24 examples with yield between 78-96% yield (**Scheme 27**) [75]



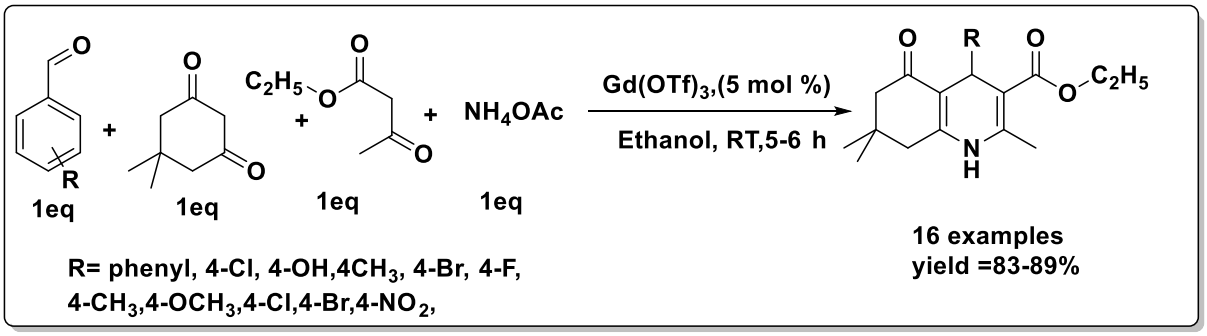
Scheme 27: Solvent free reaction reported by Davoodnia *et al*. and Khaligh. *et al.*

In 2017, Liberto.*et al*. has taken a protocol for the synthesis of 2,4-disubstituted quinolines using aromatic aldehydes, aromatic amines, styrene under at 200^0C temperature Microwave condition using $CX4SO_3H$ catalyst or at 80^0C temperature in acetonitrile solvent having 28 examples with yield between 38-78% yield (**Scheme 28**) [76]



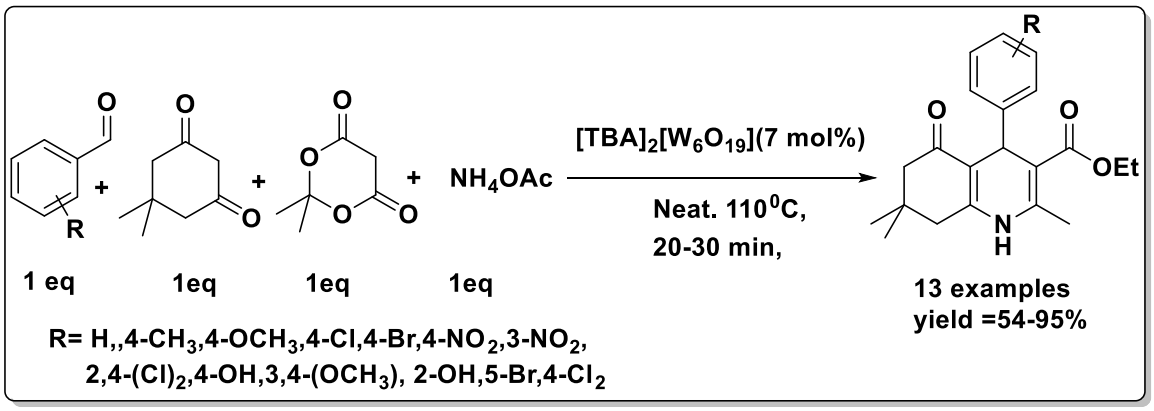
Scheme 28: Microwave assisted solvent free reaction reported by Liberto.*et al.*

In 2017, Mansoor *et al*. reported a muticomponent method by for the synthesis of hexahydeoquinolones by using $Gd(OTf)_3$ as catalyst from aldehydes , 5,5-dimethyl-1,3-cyclohexaedione dimedone, ethyl acetoacetate and ammonium acetate by using $Gd(OTf)_3$ as catalyst at room temperature. [77]. The procedure have 16 examples with yield between 83-89% yield (**Scheme 29**).



Scheme 29: Mild synthesis protocol for polyhydroquinoline in ethanol reported by Mansoor *et al.*

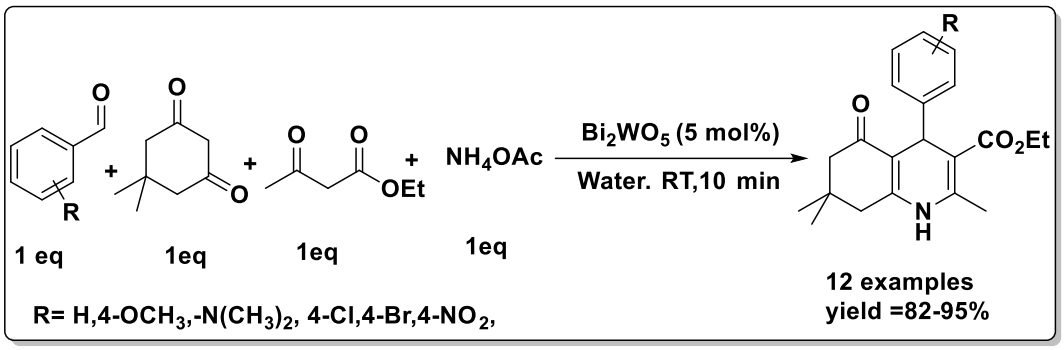
In 2011, Khojastehnezhad.*et al.* reported a synthetic method for the synthesis of hexahydroquinolinones in one-pot, four-component method taking dimedone , aldehydes , ethyl acetoacetate and ammonium acetate under solvent-free conditions using $[TBA]_2[W_6O_{19}]$ catalyst [78-79]. The procedure have 13 examples with yield between 54-95% yield (**Scheme 30**).



Scheme 30: Solvent free reaction reported by Davoodnia.*et al*. and Khaligh.

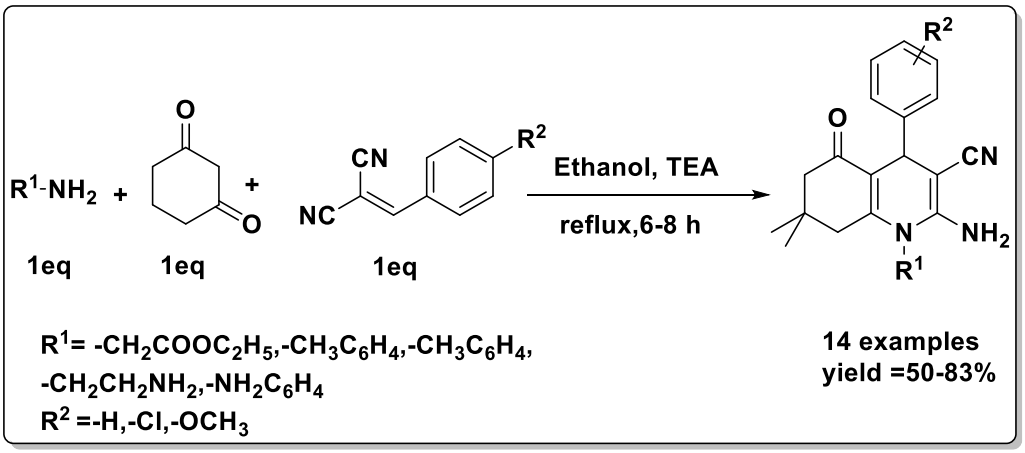
In 2014, Paplal.*et al*. synthesized different types of functionalized polyhydroquinolines by reaction of substituted aromatic aldehydes, ethyl acetoacetate, dimedone and ammonium acetate

in aqueous medium using Bi_2WO_5as catalyst having 12 examples with yield between 82-95% yield (**Scheme 31**) .[80]



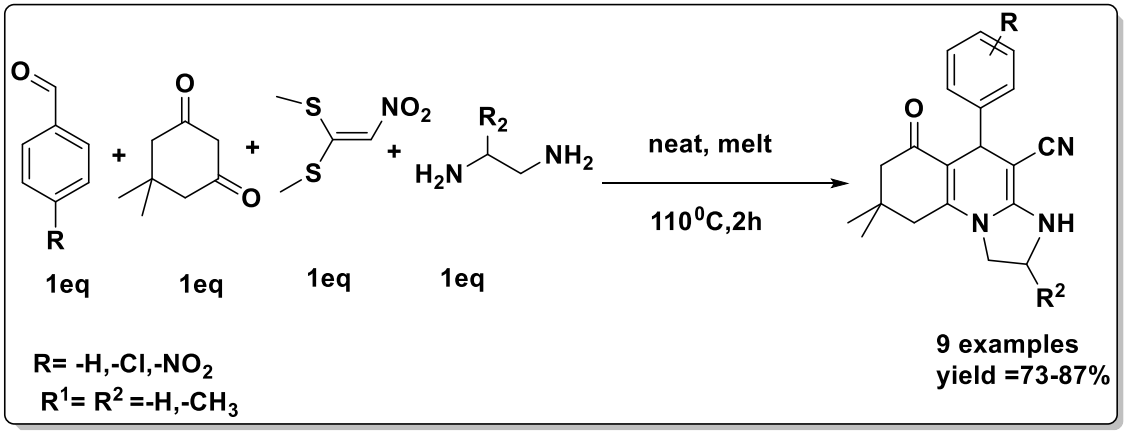
Scheme 31: Synthesis of functionalized polyhydroquinolines reported by Paplal.*et al.*

In 2017, Abdelhamid.*et al*. had made a protocol for the three-component cyclocondensation synthetic method of hexahydroquinoline derivatives from 1,3-cyclohexanedione, primary amine in presence of ethanol, TEA under reflux condition having 14 examples with yield between 50-83% yield (**Scheme 32**) . [81]



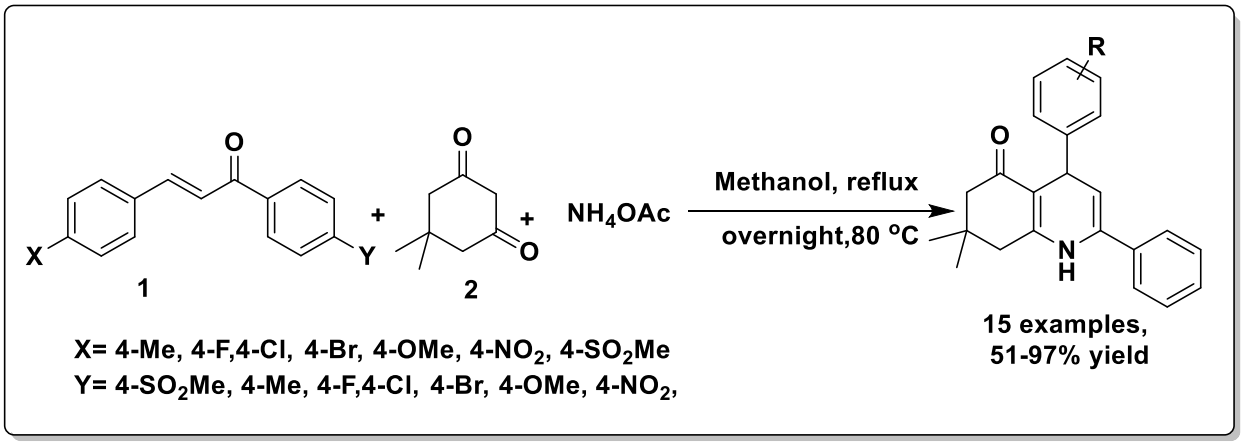
Scheme 32. Three-component cyclocondensation with TEA in ethanol reported by Abdelhamid.*et al*.

In 2014, Alizadeh.*et al.* sythesised the octahydro-imidazo[1,2-a]quinoline derivatives under solvent free conditions from aromatic aldehyde, dimidone as amazor component. The advantage of this procedure involve catalyst free reaction having 9 examples with yield between 73-87% yield (**Scheme 33**) [82].



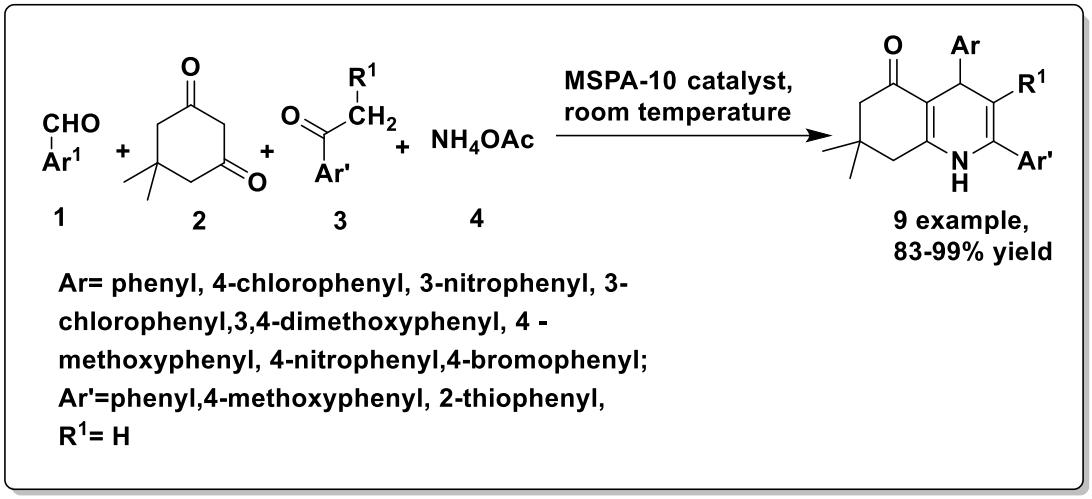
Scheme 33: Solvent free reaction reported by Alizadeh.*et al.*

In 2014, Zarghia.et al. has reported a synthesis of 2,4-diarylhexahydroquinolines by the one pot reaction between mixture of 5, 5-dimethyl-1,3-cyclohexandion, 1,3-diaryl-2-propen1-one, ammonium acetate in methanol under refluxed condition at 80^0C for overnight.This procedure have greener advantageous having 15 examples with yield between 51-97% yield (**Scheme 34**) [83]



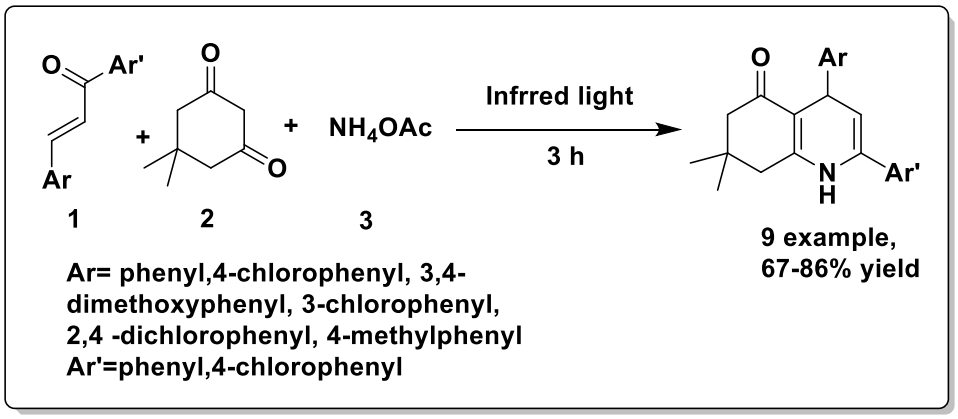
Scheme 34:. Synthesis of 2,4-diarylhexahydoquinolines by Zarghia.*et al.*

In 2013, Ray.*et al*. has reported a synthesis of 2,4-diarylhexahydroquinolines by carring out a one pot 4-component reactions between aromatic aldehydes, dimedone and acetophenone and ammonium acetate by using a new heterogeneous MCM-41 silica supported HPF_6 catalyst The procedure have some greener advantageous having 15 examples with yield between 51-97% yield. (**Scheme 35**) [84]



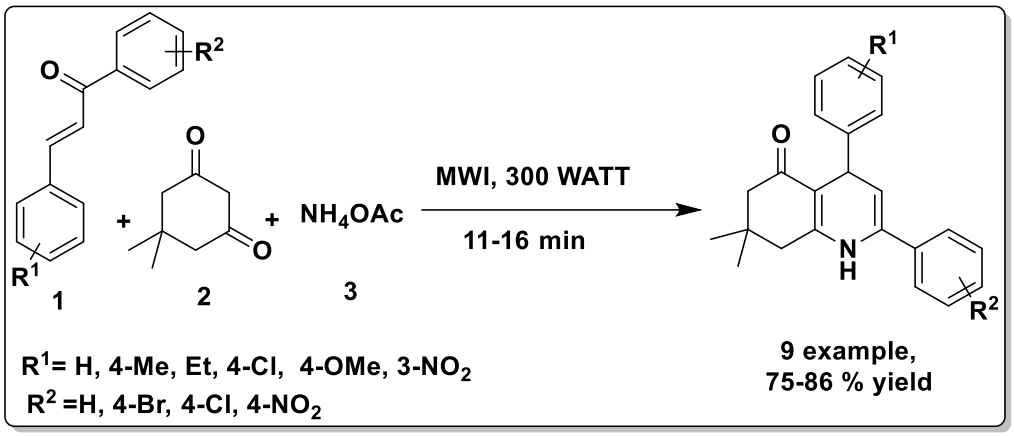
Scheme 35: synthesis of 2,4-diaryhexahydroquinolines by Ray.*et al*.

In 2006, Wang.*et al*. reported a synthetic procedure for the synthesis of 2,4-diarylhexahydroquinolines by doing a one pot 3-component reactions between Chalcones, dimedone and ammonium acetate by infrared irradiation (IR) irradiation promoted the synthesis having 9 examples with 67-86% yield (**Scheme 36**).[85]



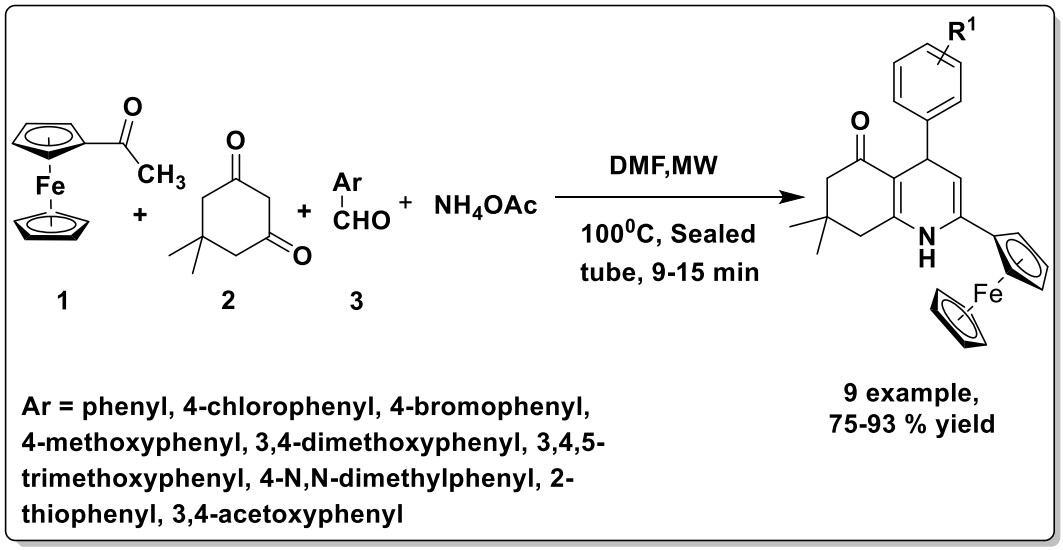
Scheme 36: synthesis of 2,4-diarylhexahydroquinolines by Wang.*et al*.

In 2005, Hua.*et al*. reported a synthetic procedure for the synthesis of 2,4-diarylhexahydroquinolines by doing a one pot 3-component reactions between Chalcones, dimedone and ammonium acetate by microwave irradiation (mwi 300 watt) the synthesis with 75-86% yield.(**Scheme 37)** [86]



Scheme 37: synthesis of 2,4-diarylhexahydroquinolines by Hua.*et al.*

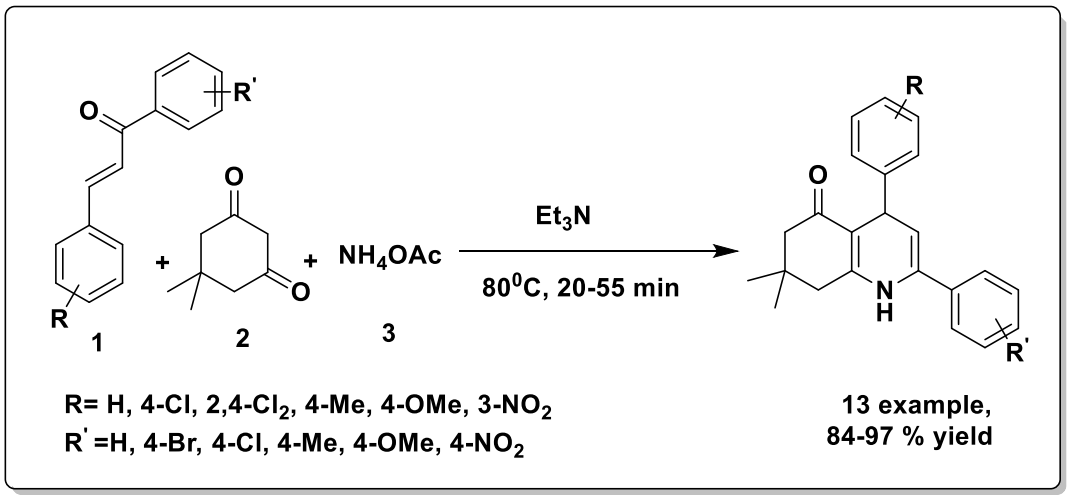
In 2009, Tu.*et al.* reported a synthetic procedure for the synthesis of 2,4-diarylhexahydroquinolines by doing a one pot 4-component reactions between aromatic aldehydes, dimedone, ammonium acetate and ferrocenyl active metheline compound by microwave irradiation (MW) in presence of DMF solvent with 75-93% yield (**Scheme 38**).[87]



Scheme 38: synthesis of 2,4-diarylhexahydroquinolines by Tu.*et al.*

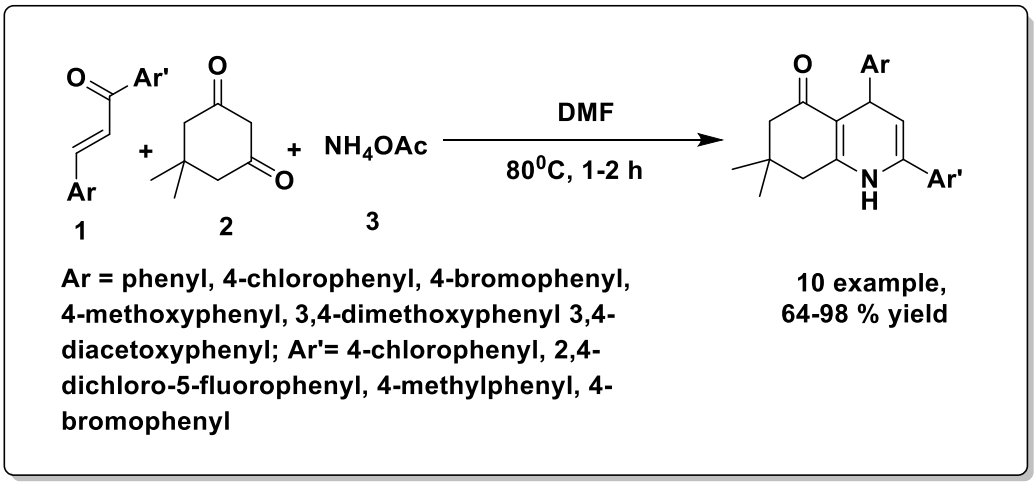
In 2015, Karimi-Jaberi.*et al.* reported a convenient and efficient protocol for the synthesis of 2,4-diaryl hexahydroquinoline derivatives by a three-component reaction between Chalcones,

dimedone and ammonium acetate catalyzed by triethylamine under solvent-free conditions with yield 84-97% (**Scheme 39**).[88]



Scheme 39: Synthesis of 2,4-diarylhexahydroquinolines by Karimi-Jaberi *et.al.*

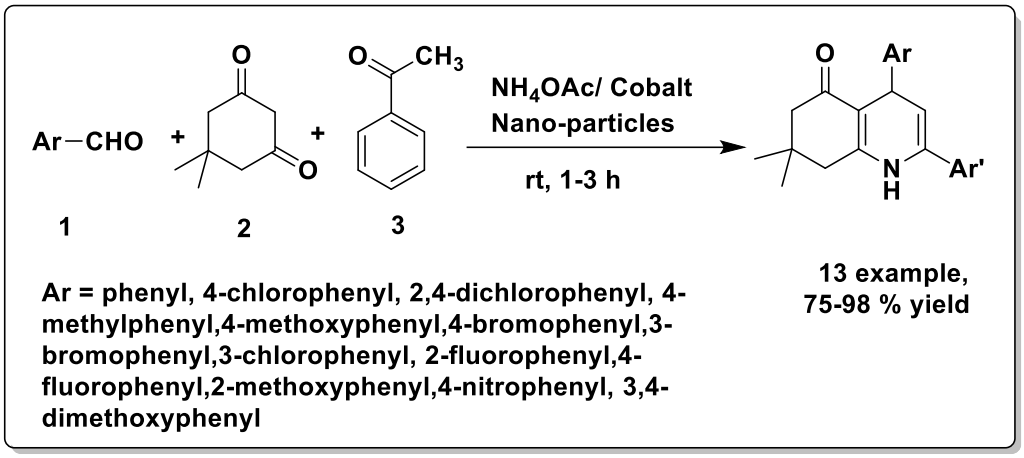
In 2002, Wang.*et al.* reported a series of substituted 2,4-diarylhexahydroquinoline derivatives by a 3-component reaction of dimedone ammonium acetate and 1,3-diaryl-2-propen-1-one (Chalcones) in DMF at 80^0C temperature with yields 64–98%. (**Scheme 40**) [89]



Scheme 40 :Synthesis of 2,4-diarylhexahydroquinolines by Wang.*et al.*

In 2011, Safari.*et al.* reported a straightforward method for the synthesis of 2,4-diarylhexahydroquinoline derivatives by the reaction between dimedone, acetophenone, aromatic

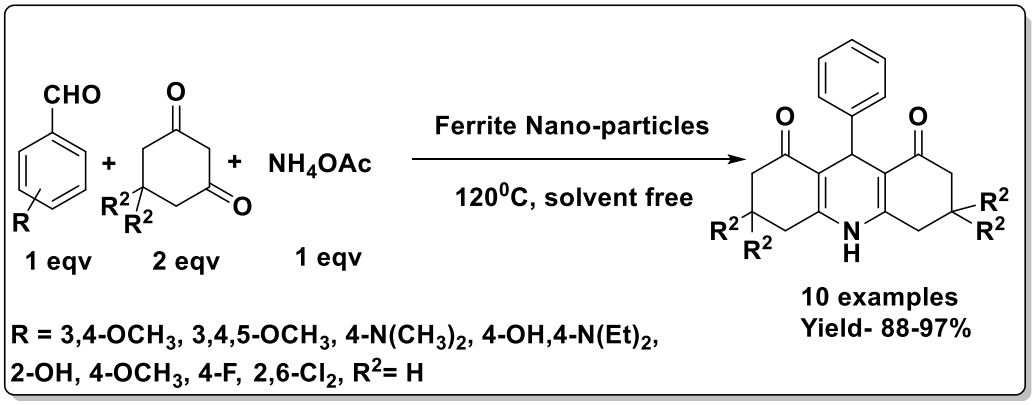
aldehydes, and ammonium acetate in the presence of a catalytic amount of Cobalt nanoparticles at room temperature with 75-98% yield (**Scheme 41**).[90]



Scheme 41: Synthesis of 2,4-diarylhexahydroquinolines by Safari.*et al.*

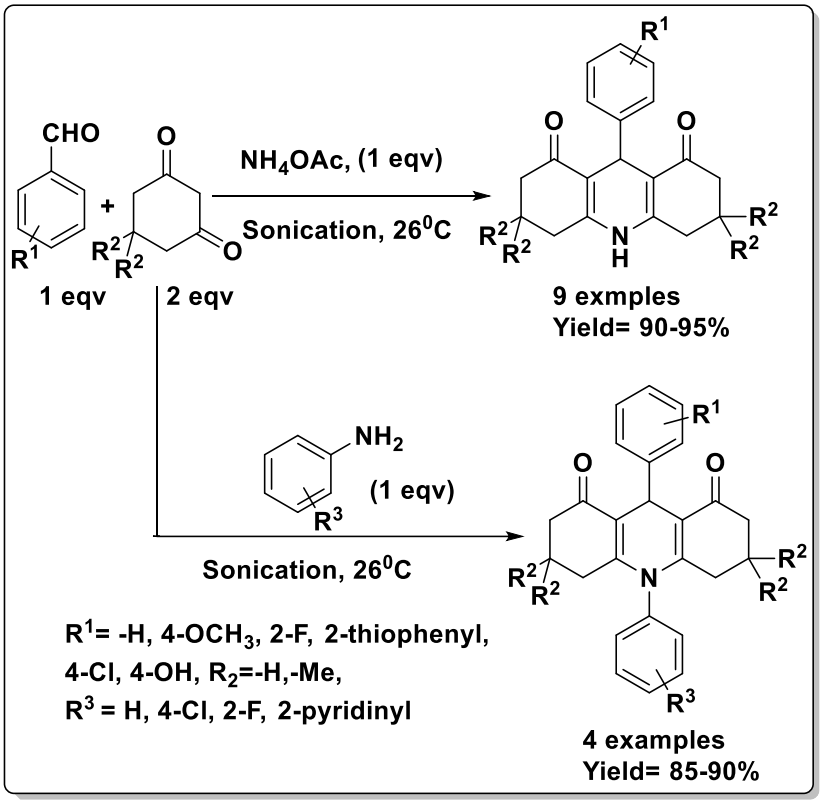
Methods synthesis of acridinedione derivatives

In 2016, Sunkara.*et al*. had done the synthesis of 9-aryl substituted acridinedione derivatives under solvent free conditions. A one-pot reaction methodology was adopted with the use of 1,3-cyclohexanedione, aldehydes and ammonium acetate using nano ferrite at 120^0C for the preparation of acridinediones and their derivativeswith yield 88-97% (**Scheme 42**).[91]



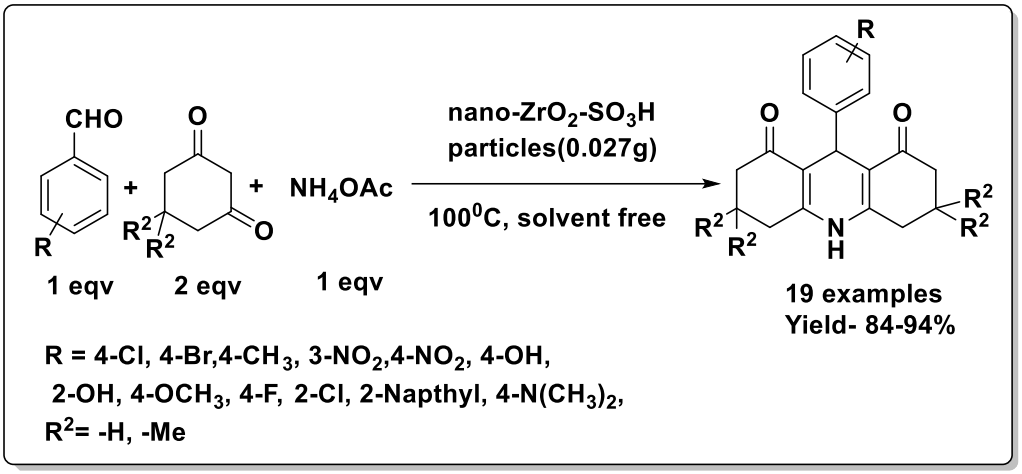
Scheme 42. One-Pot Facile Synthesis of Acridinediones and their Derivatives by Sunkara.*et al*.

In 2013, A Facile Synthesis of N-H- and N-Substituted Acridine-1,8-diones under Sonic Condition by Sudha.*et al*. Here ceric ammonium nitrate (CAN) was used along with aromatic aldehydes and aromatic amines or ammonium acetate and dimedone or cyclohexyl-1,3-diones at 26^0C under sonic condition with yield 85-90% (**Scheme 43**). [92]



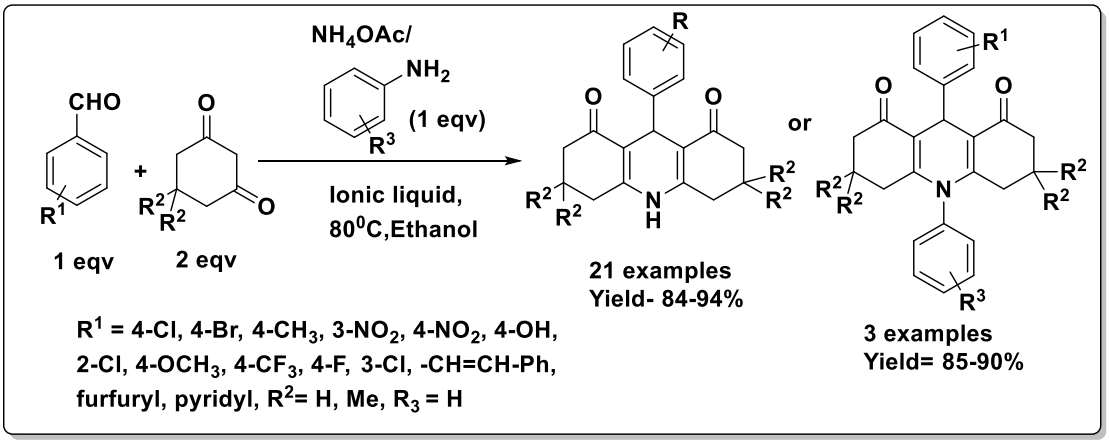
Scheme 43. A Facile Synthesis of N-H- and N-Substituted Acridine-1,8-diones by Sudha.*et al*.

In 2016, Amoozadeh.*et al.* synthesized 9-arylhexahydroacridines with taking a mixture of various 1,3-cyclic diketone, aromatic aldehydes, and ammonium acetate in presence of n-ZrSA as catalyst at 100 °C (in an oil bath) in solvent free conditions with yield 84-94% (**Scheme 44**).[93]



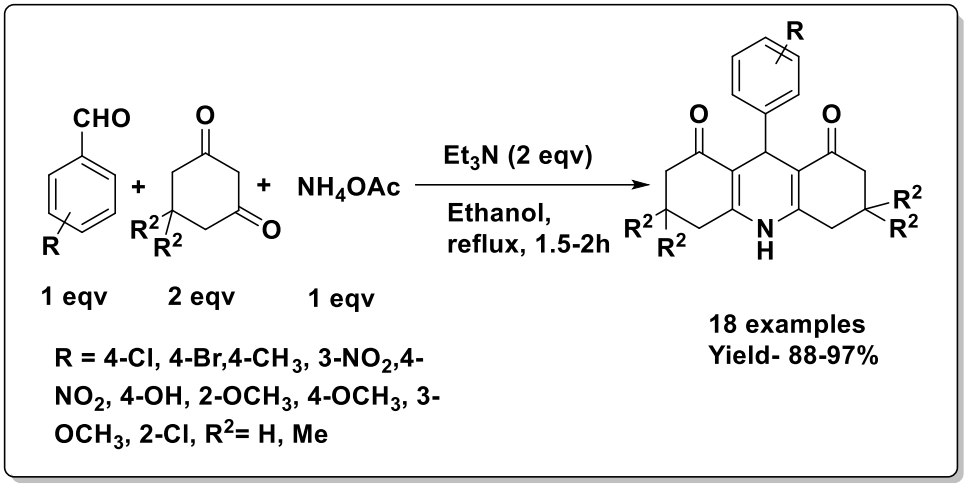
Scheme 44. Synthesis of 9-arylhexahydroacridines Amoozadeh.*et al.*

In 2017, Zhu.*et al*. reported the synthesis of 9-arylhexahydroacridines using aromatic aldehyde, 5,5-dimethyl-1,3-cyclohexanedione, NH_4OAc and corresponding amount of ionic liquid were mixed with 1 ml ethanol, and then heated at 80^0C by using a series of ionic liquids based on betainium cation (Hbet) with different anions with yield 84-94% (**Scheme 45**).[94]



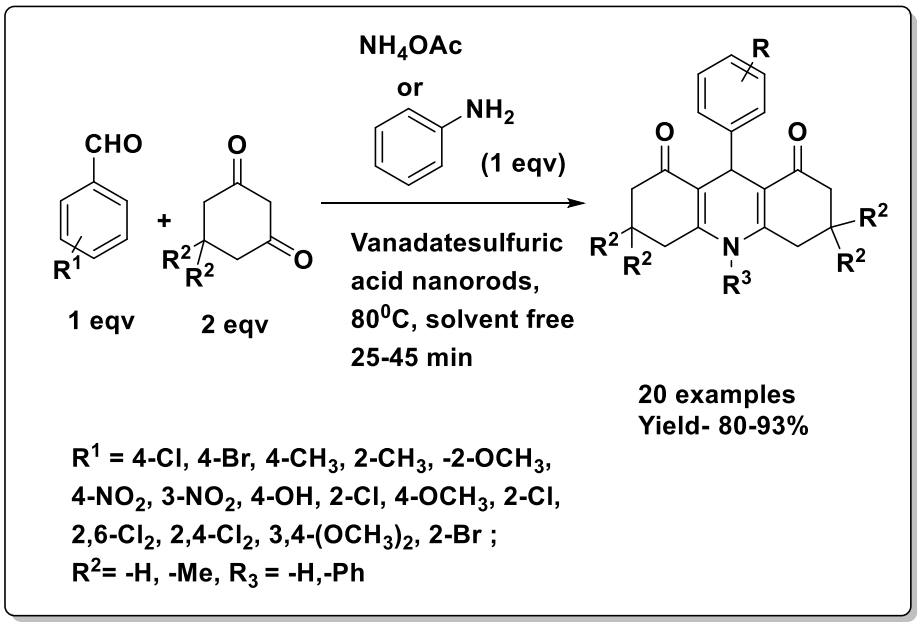
Scheme 45. Synthesis of 9-arylhexahydroacridines Zhu.*et al*.

In 2018, Djemoui.*et al.* reported an efficient approach to the synthesis of 1,8-dioxo-decahydroacridines via one-pot multi-component condensation of an aromatic aldehyde, cyclic 1,3-diketones and NH_4OAc in ethanol with use of Triethylamine (TEA) at reflux condition wth yield 88-97% (**Scheme 46**).[95]



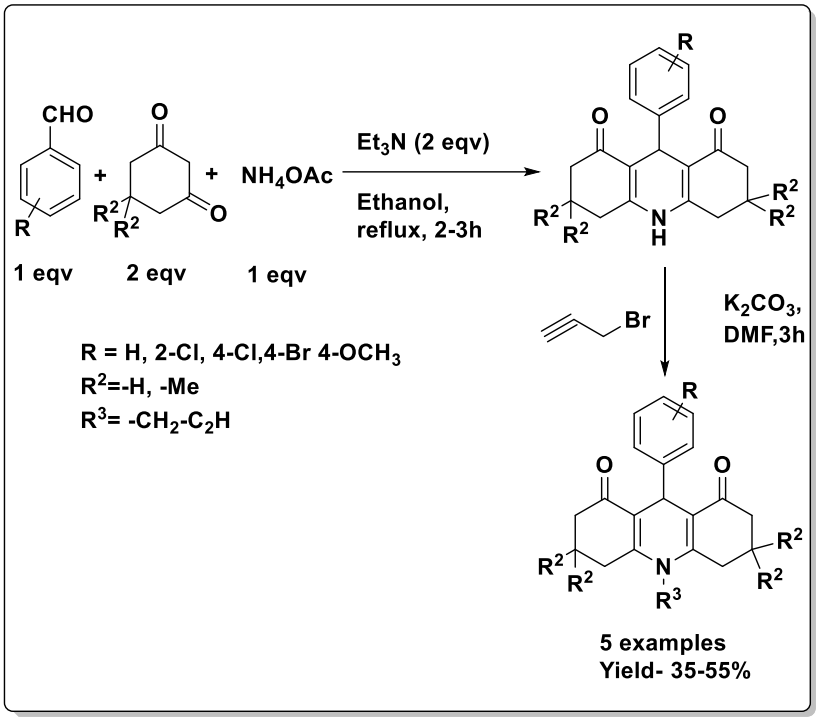
Scheme 46: An efficient synthetic approach to the synthesis of 1,8-dioxo-decahydroacridines by Djemoui.*et al.*

In 2015, Nasr-Esfahani.*et al.* reported a synthesis of hexahydroacridine-1,8-diones using 1,3- cyclohexanedione derivatives, aldehydes and ammonium acetate or aniline under solvent-free conditions. Nanorod vanadatesulfuric acid (VSA-NRs), was used as catalyst as a novel, recyclable and eco-benign catalyst to synthesis hexahydroacridine-1,8-diones with yield 80-93% (**Scheme 47**). [96]



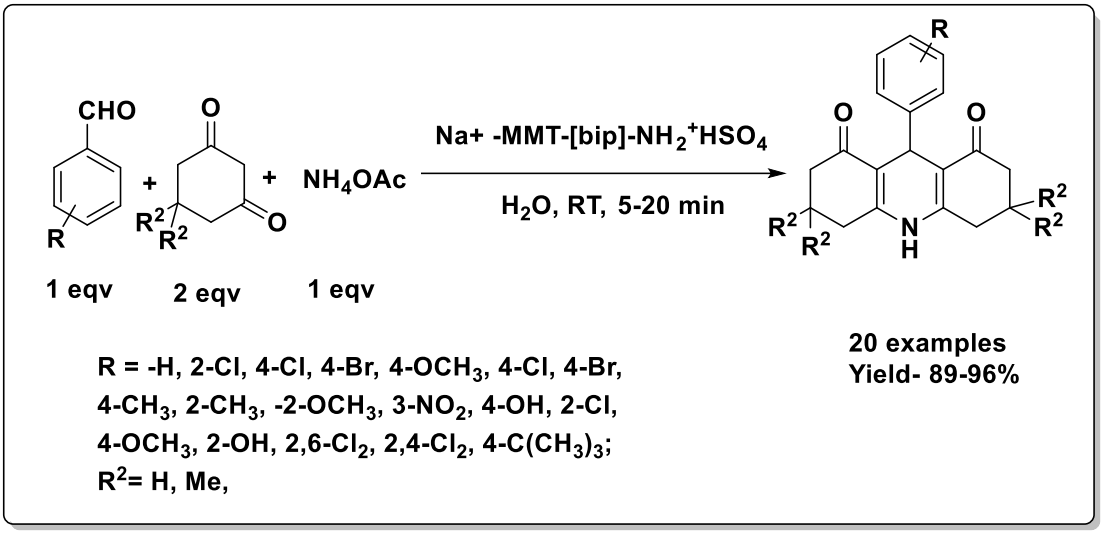
Scheme 47: Nasr-Esfahani.*et al.* reported a synthesis of hexahydroacridine-1,8-diones

In 2020, Naouri.*et al.* reported a procedure for the preparation of 1,8-dioxodecahydroacridine derivatives via a one-pot three-component condensation of aromatic aldehydes, 1,3-cyclohexanedione and ammonium acetate in ethanolic medium under reflux condition catalyzed by triethylamine (TEA) to give the desired productwith yield 35-55% (**Scheme 48**).[97]



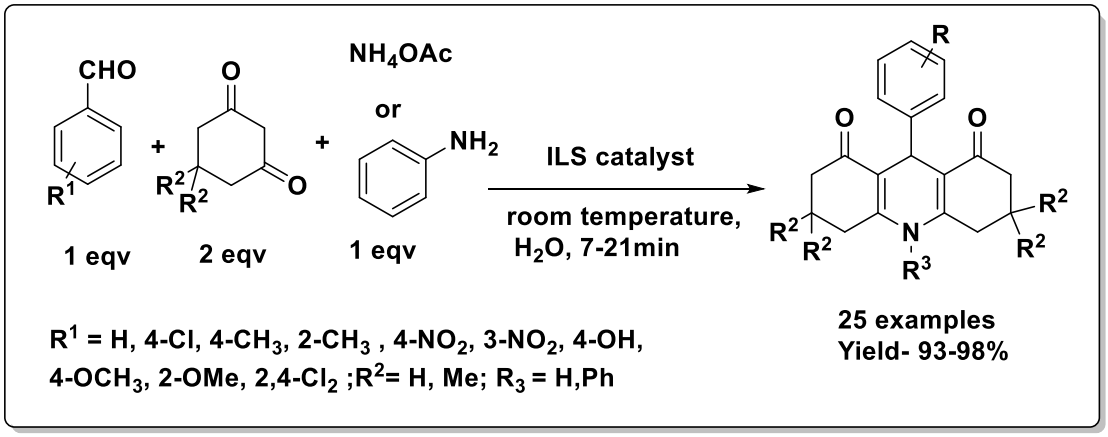
Scheme 48: A one pot multicomponent synthesis of 1,8- dioxodecahydroacridine derivatives by Naouri.*et al.*

In 2020, Mazloumi.*et al.* reported the synthesis of 1,8-dioxo-decahydroacridines via Hantzsch condensations using a new nanoporous catalyst formulated as Na^{+} -MMT-[bip]-NH_2 $^{+}$ HSO_4. All reactions were performed under mild reaction conditions taking mixture of a β-ketoester derivative, 1,3-cyclohexanedione derivatives, aldehyde and ammonium acetate with yield 89-96% (**Scheme 49**). [98]



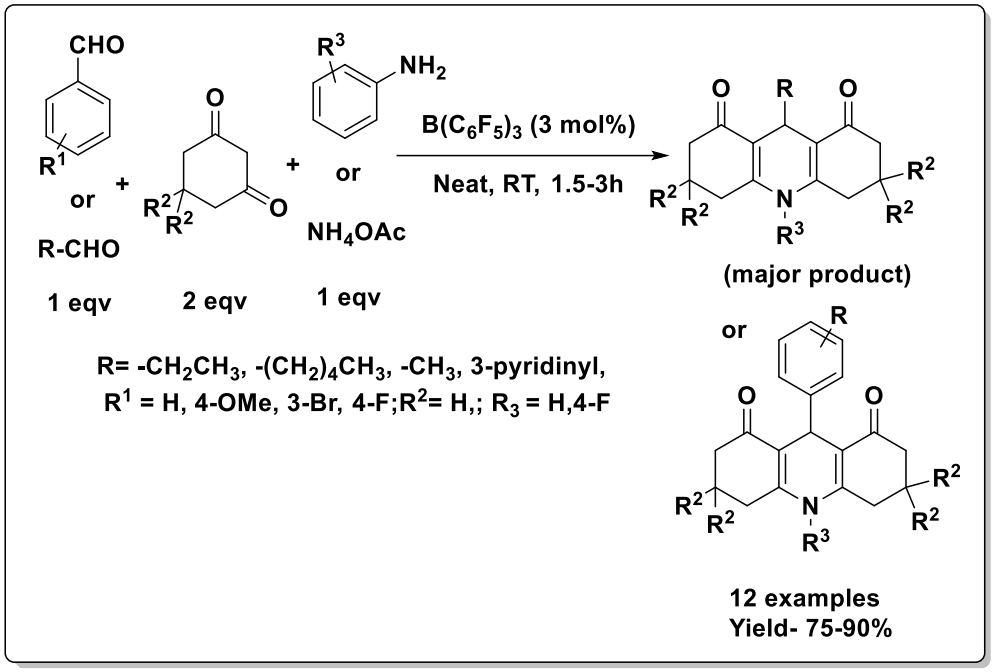
Scheme. 49: Synthesis of 1,8-dioxo-decahydroacridines by Mazloumi.*et al.*

In 2011, Vahdat.*et al.* had synthesised 1,8-dioxodecahydroacridines by using ionic liquid with multi-SO_3H groups attached with it via the one-pot method with excellent yield within at room temperature in water medium with yield 93-98% (**Scheme 50**).[99]



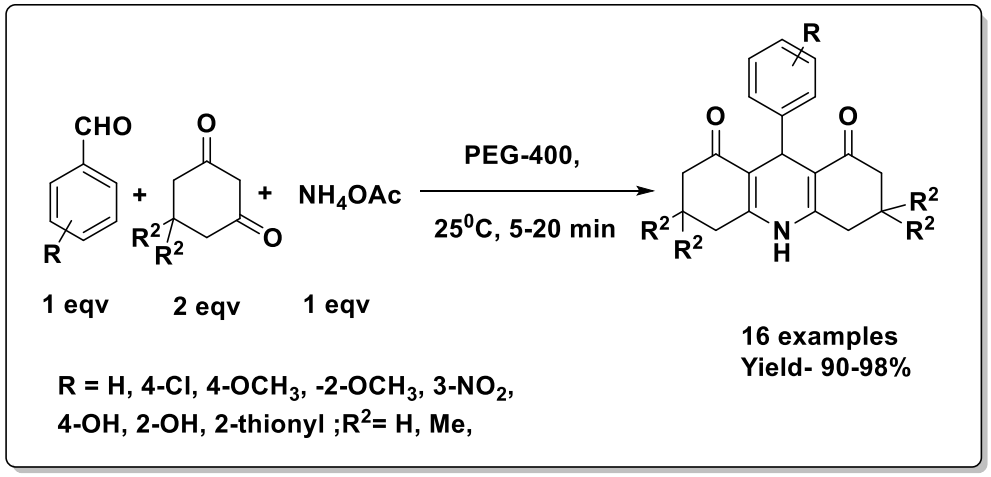
Scheme 50: Synthesis of 1,8-dioxo-decahydroacridines by Vahdat.*et al.*

In 2008, A mild and efficient method for the synthesis of 1,8-dioxodecahydroacridines has been developed by Chandrasekhar.*et al.* via a three-component reaction of a cyclic 1,3-dione, an aldehyde and an amine, under solvent-free conditions, at room temperature catalyzed by tris(pentafluorophenyl)borane [$B(C_6F_5)_3$]with yield 75-90% (**Scheme 51**).[100]



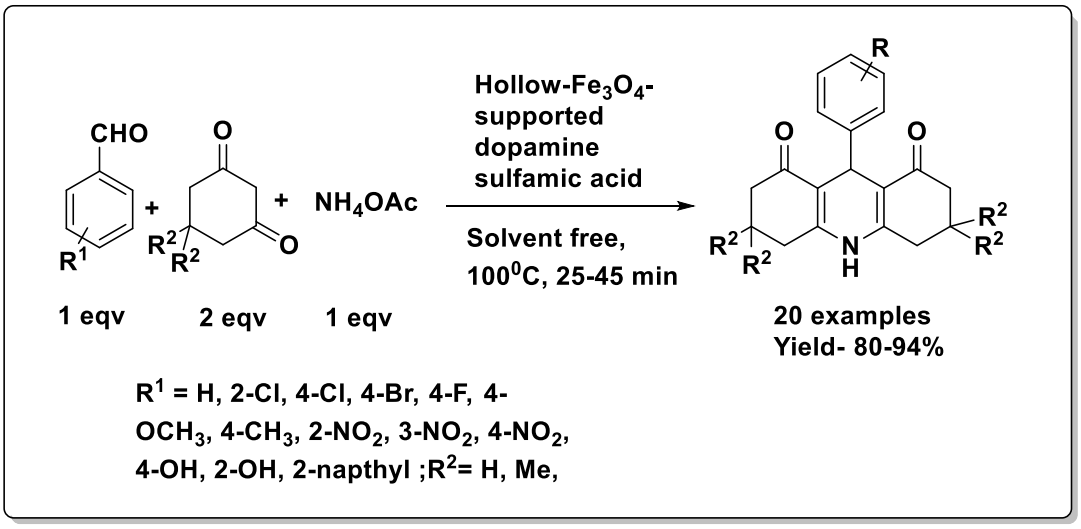
Scheme 51: A mild and efficient method for the synthesis of 1,8-dioxodecahydroacridines by Chandrasekhar.*et al.*

In 2010, Kidwai.*et al.* synthesized decahydroacridine-1,8-diones in the presence of polyethylene glycol (PEG) which was found to be an inexpensive non-toxic and effective medium for one pot synthesis of the product with higher yields up to 90-98% (**Scheme 52**). [101]



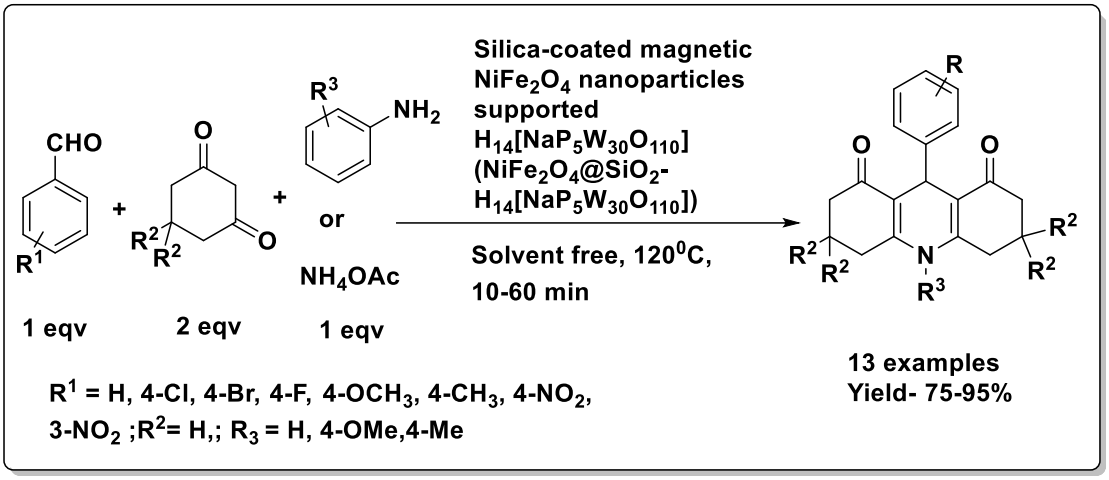
Scheme 52: Synthesis of 1,8-dioxodecahydroacridines has been developed by Kidwai.*et al.*

In 2017, Mirhosseyni.*et al.* reported the synthesis of 1,8-dioxodecahyroacridine derivatives using H-Fe_3O_4@DA-SO_3H as catalyst by using aldehyde , ethyl acetoacetate or 1,3-cyclohexanedione NH_4OAc at 100^0C under solvent-free condition with yield 80-94% (**Scheme 53**).[102]



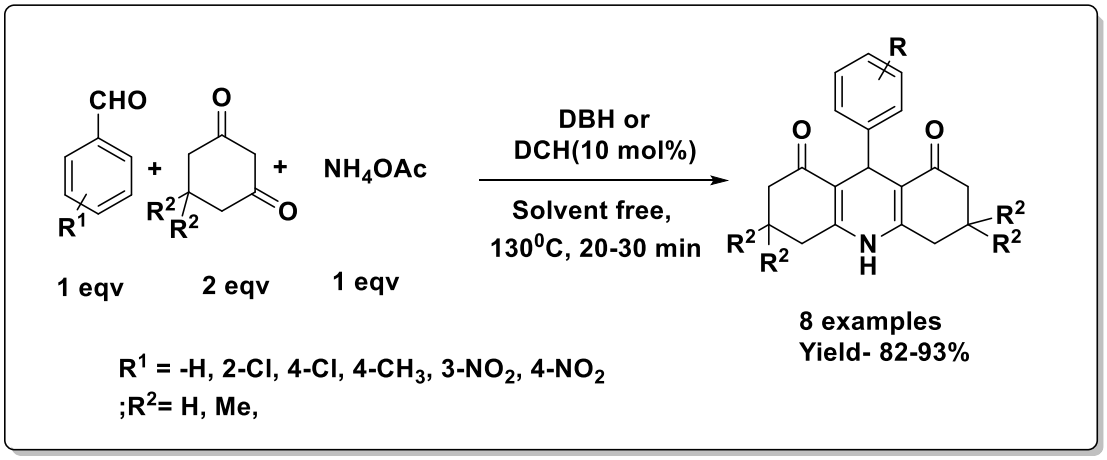
Scheme 53: Synthesis of 1,8-dioxodecahyroacridine derivatives Mirhosseyni.*et al.*

Malekia.*et al.* designed a method by using silica-coated magnetic $NiFe_2O_4$ nanoparticles-supported $NiFe_2O_4$@SiO_2-$H_{14}[NaP_5W_{30}O_{110}]$ as versatile and highly efficient heterogeneous catalyst for one-pot multicomponent synthesis of 1,8-dioxodecahyroacridine derivatives under solvent-free condition. The synthesized catalyst can be magnetically recovered and reused four times without significant loss in catalytic efficiency with yield 75-95% (**Scheme 54**).[103]



Scheme 54: synthesis of 1,8-dioxodecahyroacridine derivatives by Malekia.*et al.*

Solvent free one pot synthesis of 1,8-dioxodecahydro acridine derivatives have been described by Maleki.*et al*. via Hantzsch condensation of various aldehydes, ammonium acetate,cyclic 1,3-dicarbonyl compounds in a very simple, efficient and environmentally benign method with excellent yield up to 93% (**Scheme 55**). [104]



Scheme 55: Solvent free one-pot synthesis of 1,8-dioxodecahydroacridine derivatives by Malekietr.*et al.*

Conclusion

Quinolines, acridines and its derivatives are an imperative heterocyclic ring system, having pharmacological applications in medicinal chemistry. Therefore, there is an unceasing search of environmental-friendly methods to its synthesis. The review compiled and organized most of the newer methods documenting their advantages, limitations and substrate scope and this will help to plan further investigation in this subject. The category wise design and discussions on the advancements will draw a clear picture to the researchers lobby about the advantages and importance of each category and so they could use and improve current methodologies.

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