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A Review on Methods of Synthesis of Quinazolines and (4*H*)-3,1-Quinazolin-4-ones

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ABSTRACT

The main objectives of organic and medicinal chemistry are the design, synthesis and production of molecules having valuable human therapeutic effects. There are numerous biologically active molecules with six-membered rings, containing two heteroatoms. The development of research on biological activity of quinazoline compounds started with the synthesis of 2-methyl-3-phenylquinazolin-4(3*H*)-one that was later on approved to have has soporific and sedative action. This biological importance encouraged scientists to develop various new synthetic pathways of novel products. This review may cover and explain most of the old and recent synthetic methods of quinazolines and quinazolinones over more than a century.

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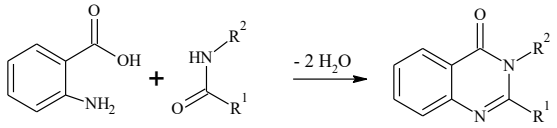
1. Introduction

Quinazoline is a fused bicyclic compound earlier known as benzo-1,3-diazine. It was first prepared in the laboratory in 1903 (Gabriel, 1903) The 4-(3*H*)-Quinazolinone (s) is condensation products of anthranilic acid and amides and they can also be prepared in this fashion through the *Nimentowskyquinazolinone synthesis* (Abdullah et al., 2011)(Scheme 1).

1.1 Classification of Quinazolines and Quinazolinones

Based on our current review, the syntheses of both quinazolinones and quinazolinescan be classified into the following categories according to the substitution patterns of the ring system (Fig. 1):

i. 2-Substituted-4(3*H*)-quinazolinones and -quinazolines.
ii. 3-Substituted-4(3*H*)-quinazolinones.
iii. 4-Substituted-quinazolines.
iv. 2,4-Disubstituted quinazolinone.
v. 2,4-Disubstituted quinazolines.



Scheme 1. Synthesis of 4-(3*H*)-quinazolinone

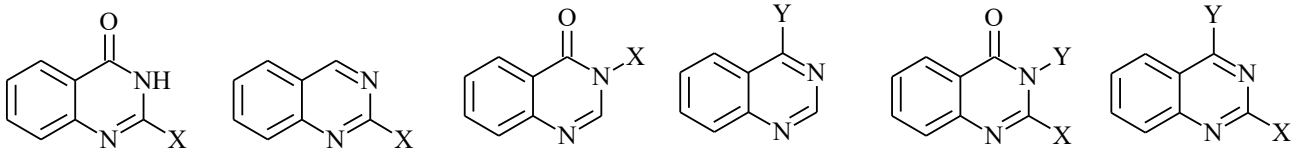


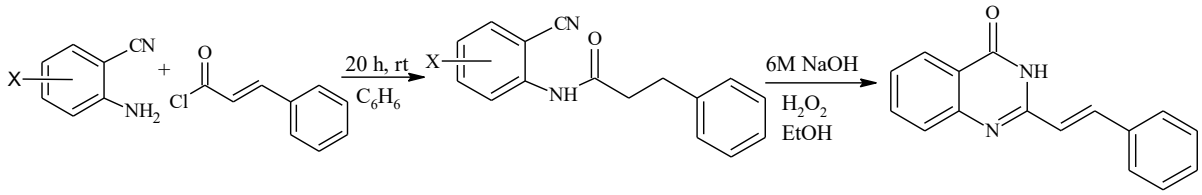
Fig 1. Classification of synthesis of quinazolinones and quinazolines

1.1.1. 2-Substituted Quinazolinones

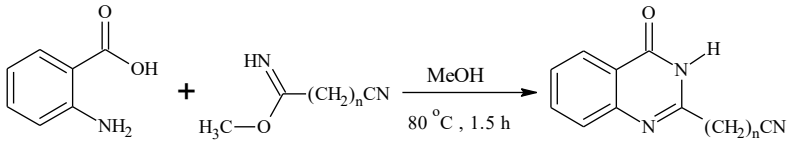
The most common approach involves amidation of 2-aminobenzonitrile, 2-aminobenzoic acid and 2-amino benzamide. As an example, the reaction of 2-aminobenzonitrile with 3-phenylacryloyl chloride followed by oxidative ring closure under basic conditions produced 2-styryl-4(3*H*)-quinazolinone in 29% yield (Bogert et al.,1902, Bogert et al.,1903, Taylor et al.,1960, Irwin et al.,1965) (Scheme 2).

The reaction of anthranilic acid with imidates in methanol at 80 ^{0}C affords the desired quinazolinones in good yields (Ried et al.,1963-*a*, Ried et al., 1962, Ried et al., 1963-*b*) (Scheme 3).Gruner et al.(2000)developed a novel route to 2-alkylthio-quinazolines by heating a suspension of *N*-chloro-acetylanthranilic acid ethyl ester with potassium thiocyanate in acetonitrile (ACN).

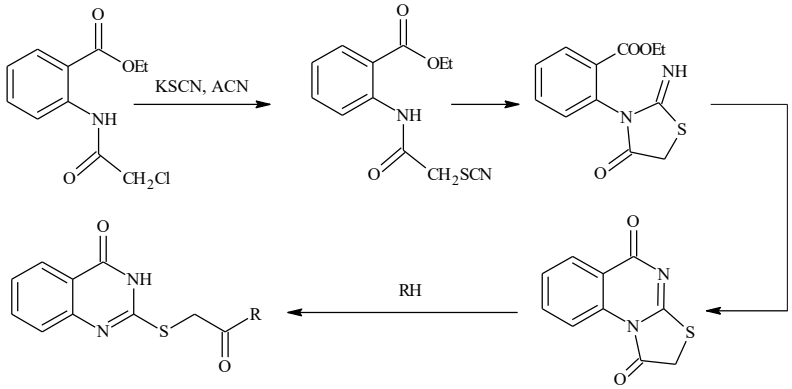
It was discovered that the alcohol or amine employed as the solvent reacted with the thiazolo (Bogert et al., 1902, Abdullah et al., 2011) quinazoline-1, 5-dione intermediate to furnish the corresponding 4-oxo-3,4-dihydroquinazolines in 43–72% yield (Gruner et al., 2000)(Scheme 4).



Scheme 2. Synthesis of 2-styryl-4(3*H*)-quinazolinone



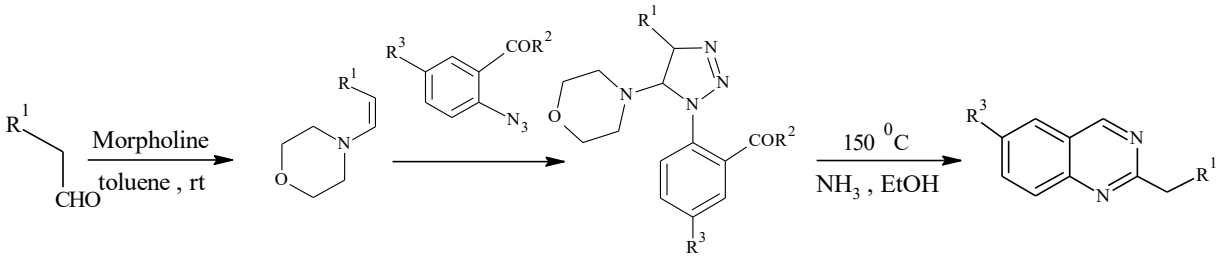
Scheme 3. Reaction of anthranilic acid with imidates to synthesize quinazolinones



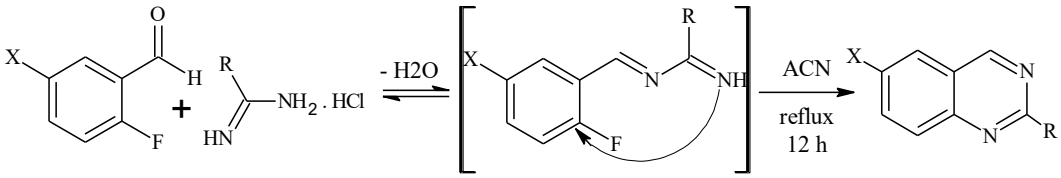
Scheme 4. Synthesis of alkylthio-quinazoline

2-Substituted Quinazolines

A three-component reaction was performed to synthesize 2-alkylquinazolines from the reaction of amidines with ammonia. In the first step, an aldehyde is reacted with morpholine and, subsequently, with an aryl azide to afford the triazolines in acceptable yields (Erba et al., 1999) (Scheme 5).Kotsukiet al.,(1999)developed a condensation of cyano- and nitro activated *o*-fluorobenzaldehydes with amidines to give a variety of quinazoline derivatives in good yields. This method involves tandem imine formation with the aldehyde function and an intra-molecular nucleophilic aromatic substitution at the fluorine-substituted carbon centre. The reaction is carried out in refluxing acetonitrile with potassium carbonate in the presence of powdered molecular sieves, and the crude product is purified by chromatography (Kotsuki et al.,1999) (Scheme 6).



Scheme 5. Synthesis of 2-alkylquinazolines

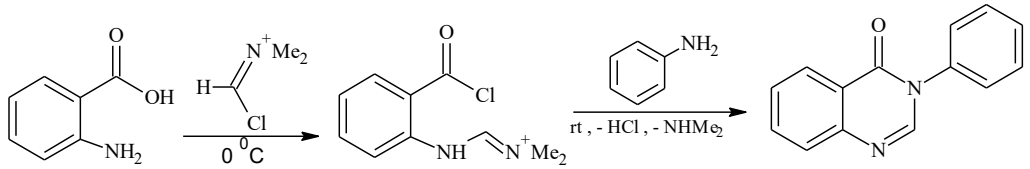


Scheme 6. Condensation of cyano and nitro activated *o*-fluorobenzaldehydes with amidines

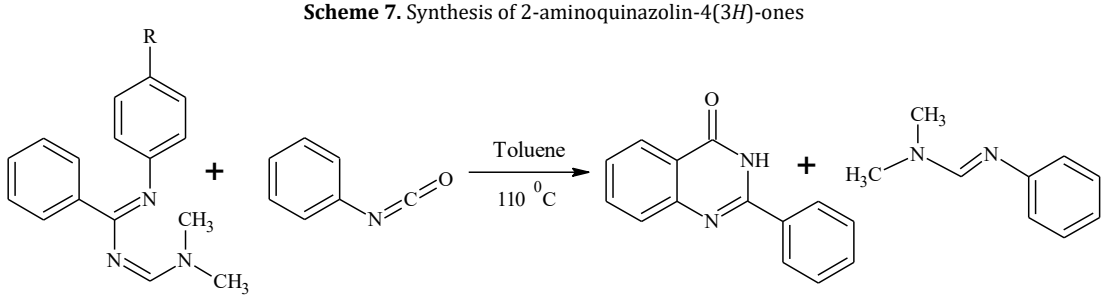
3-Substituted Quinazolinones

A concise and efficient solid-phase synthesis of 2-amino-quinazolin-4(3*H*)-ones was reported by Yang and Kaplau, involving the reaction of polymer-bound isothioureas with

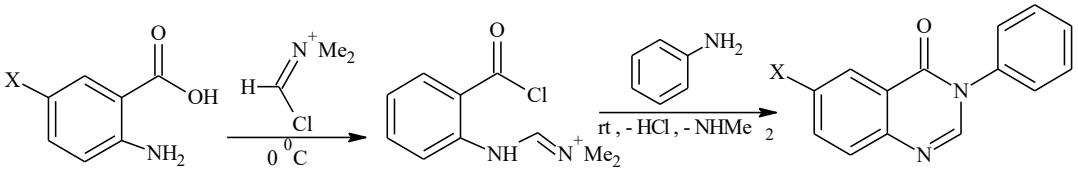
isatoicanhydride derivatives with good yields and excellent purity (Yang et al.,2000) (Scheme 7).The synthesis of 2-substituted-quinazolinones by the cyclisation of 1-aryl-4-dimethylamino-2-phenyl-1,3-diaza-1,3-butadienes and phenyl isocyanate was reported by Croce et al., (1997). The reaction was carried out under atmospheric nitrogen in toluene at reflux temperature to furnish the desired products in good yields (Croce et al., 1997) (Scheme 8).A novel dimerisation reaction to furnish 3-substituted-4(3*H*)-quinazolinones in high yield was developed by Perumal*etal*. by treating 5-substituted-2-amino-benzoic acid derivatives with the Vilsmeier reagent (Majo et al., 1996) (Scheme 9).



Scheme 7. Synthesis of 2-aminoquinazolin-4(3*H*)-ones



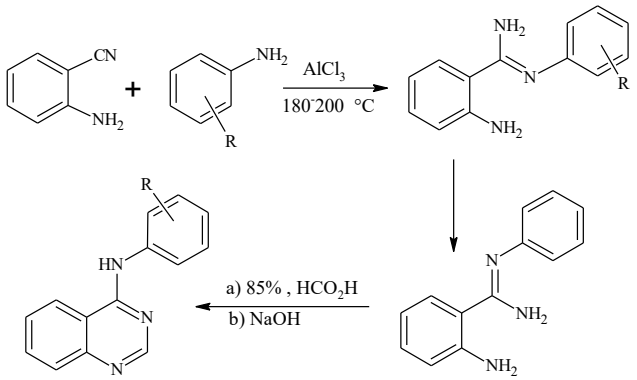
Scheme 8. Synthesis of 2-substituted quinazolinones by Croce et al



Scheme 9. Synthesis of 3-substituted-4(3*H*)-quinazolinones

1.1.2. 4-Substituted Quinazolines

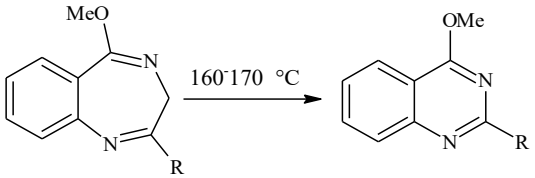
The 2-amino-*N*-arylbenzamides furnished the 4-arylamin-oquinazolines in good yields (70–92%) when heated with 85% formic acid. Later, this route was modified to enable the preparation of 2-aryl-4-aminoquinazolines (Szczepankiewiczet al., 2000, Szczepankiewicz et al., 1998) (Scheme 10).



Scheme 10. Synthesis of 4-arylaminoquinazolines

2,4-Disubstituted Quinazolines

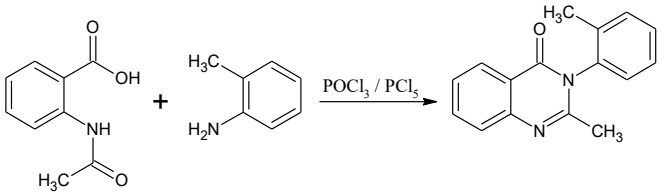
Kaname et al studied the thermolysis of 5-methoxy- and 5-diethylamino-(3*H*)-1,4-benzodiazepines to give 4-methoxy- and 4-diethylaminoquinazolines by a ring contraction mec-hanism (Kaname et al., 1999). On heating 5-methoxy-(3*H*)-1,4-benzodiazepines in diphenyl ether at 160-170°C for 6 h, 4-methoxyquinazolines were furnished as the sole products in moderate yields (41-46%) (Scheme 11).



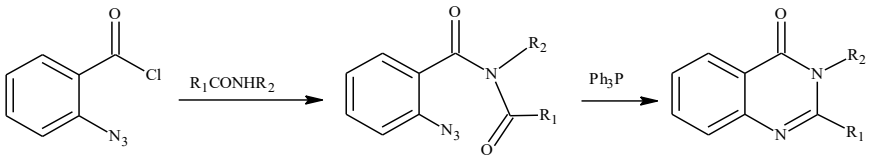
Scheme 11. Synthesis of 4-methoxyquinazolines

1.1.1. 2,3-Disubstituted Quinazolinones

Methaqualone, a sedative hypnotic, was prepared by the fusion of *N*-acetyl anthranilic acid with *o*-toludine using $POCl_3$ or PCl_5 as catalyst to facilitate the reaction more smoothly (Mattner *et al* 1973) (Scheme 12).Acylation of amide with 2-azidobenzoyl chloride forms an imide which upon treatment with tri-phenylphosphine in the course of consecutive Staudinger reac-tion/intramolecular aza-wittig reaction quantitatively give 2,3-disubstituted-quinazolin-4(3*H*)ones (Eguchi 2005, Takeuchi et al., 1989a-b)(Scheme 13).

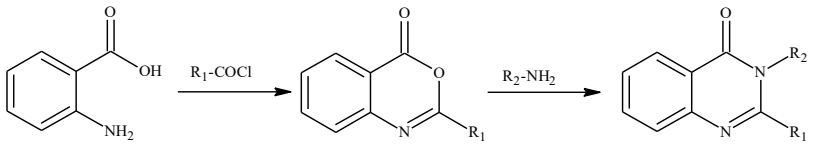


Scheme 12. Synthesis of methaqualone

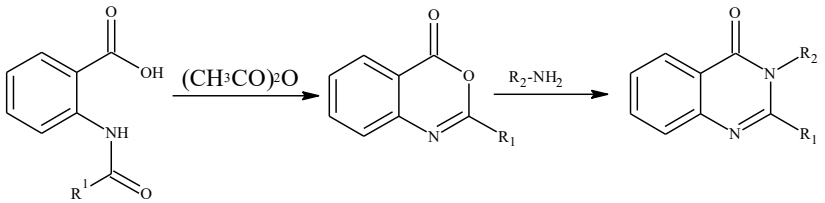


Scheme 13. Synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones using amides

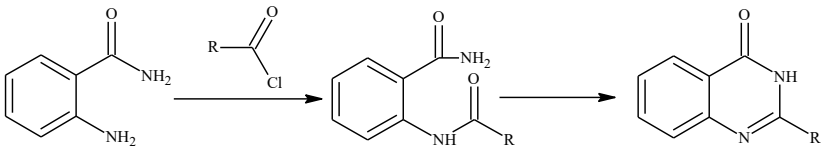
Anthranilic acid on reaction with acid chloride also forms benzoxazinone which on reaction with primary amine yield 2,3-disubstituted-quinazolin-4(3*H*)ones (Acharyulu et al., 2008, Ameta et al., 2006)(Scheme 14). Acetanthranil (3,1,4-benzoxazinone) can be easily prepared by heating anthranilic acid or a substituted anthranilic acid with an acid anhydride. Zentmayer and Wagner developed a convenient and fairly general procedure for preparation of acylanthranils or 3,1,4-benzoxazinone (Zentmayer et al 1949). 2-Amidobenzoic acid on refluxing with acetic anhydride yield benzoxazinone, which reacts exothermally with ammonia and most amine in aqueous media to give high yield of quinazolin-4(3*H*)ones (Zhou et al 2004, Patel et al., 2002, Parmar et al., 1968). Reactions of substituted aromatic amine with acetanthranil have been extensively studied (Erred et al., 1976, 1977a-b)(Scheme 15).The synthetic methodology commence with the synthesis of anthranil amide by the oxidation of 2-amino benzonitrile, followed by its amidation using acid chloride and triethylamine to give the uncyclized amide intermediate, which on oxidative ring closure under basic conditions, using potassium hydroxide yield 2-substituted-quinazolin-4(3*H*)ones (Roy et al., 2006, Witt et al., 2000, Bergman et al., 1990) (Scheme 16).



Scheme 14. Synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones using acyl chlorides



Scheme 15. Synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones using anhydride



Scheme 16. Utilizing of anthranil to synthesis of 2-substituted quinazolin-4(3*H*)-ones

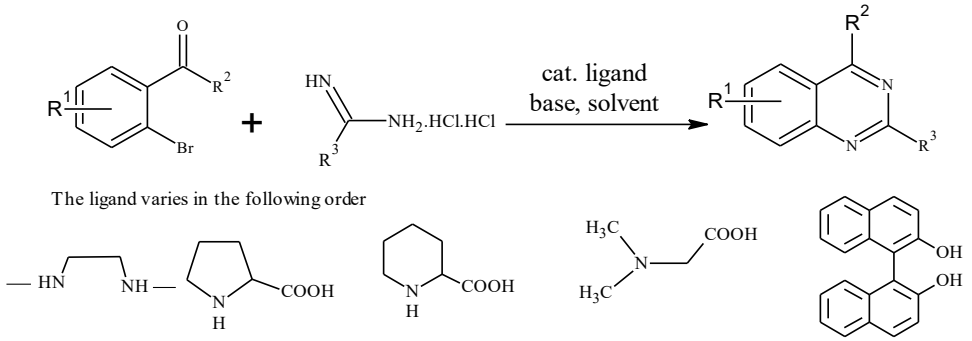
1.1.1. Miscellaneous Metal-Catalyzed Syntheses of Quinazolines

A copper-catalyzed cascade method of coupling reaction of 2-bromobenzaldehyde with acetamidine hydrochloride with optimized conditions has been made (Jiang et al., 2008) (Scheme 17).2-Arylquinazolines were synthesized from 2-amino-benzophenones and benzylic amines in good yields using ceric ammonium nitrate (CAN)-TBHP in acetonitrile (Kamakar*et al* 2011) (Scheme 18).

Another cascade copper-catalyzed reaction of (2-amino-phenyl) methanol with aryl aldehydes using a combination of cerium nitrate hexahydrate and ammonium chloride to give substituted quinazolines (Chen et al., 2013) (Scheme 19). Substituted (2-bromophenyl) methylamines and amidine hydrochlorides reacted as starting materials using CuBr as a catalyst, and air as the oxidant at 100 ^{0}C for 24 h and with DMSO as solvent (Liu et al., 2013) (Scheme 20).

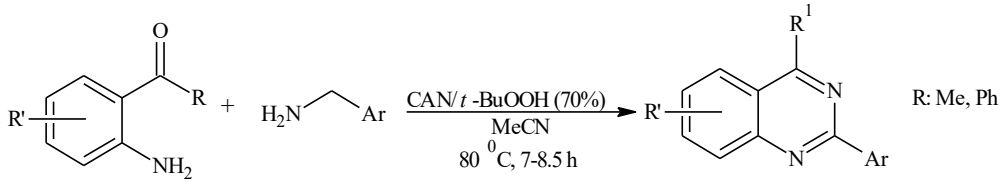
Substituted (2-bromophenyl)methylamines and amides reacted via simple ligand-free copper-catalyzed approach to quinazoline derivatives using the cascade reaction including a sequential Ullmann-type coupling and aerobic oxidation (Wang et al., 2010) (Scheme 21). A one-pot reaction of aldehydes with 2-aminobenzylamines and 2-aminobenzyl alcohols enabled efficient aerobic oxidative products in good yields (Han et al., 2012) (Scheme 22).

4-arylquinazolines were obtained in good yield in two-step reaction in the presence of TsCl and under mild conditions starting with palladium catalyzed arylation of quinazolin-4-ones with aryl boronic acids (Qiu et al., 2013) (Scheme 23).

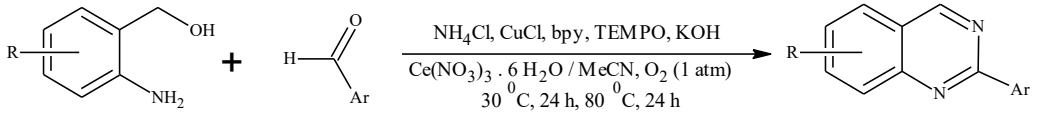


The catalyst is either CuI or CuBr and the base may be $CsCO_3$ or Na_2CO_3 or K_3PO_4 and the solvent is mostly DMF

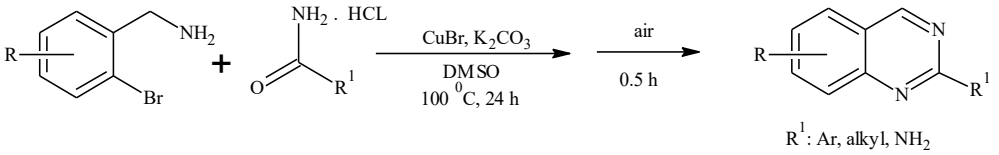
Scheme 17. Copper-catalyzed method



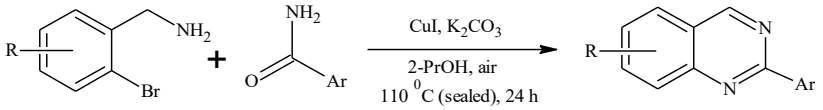
Scheme 18. Synthesis of 2-arylquinazolines from 2-aminobenzophenones



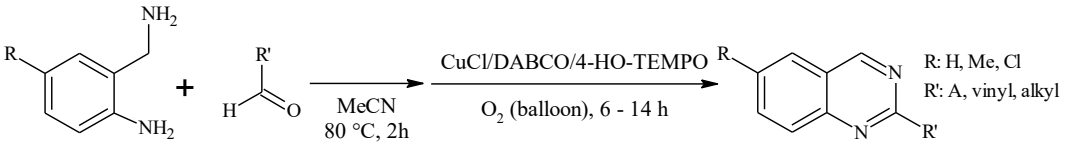
Scheme 19. Cascade copper-catalyzed reaction of (2-aminophenyl)methanol



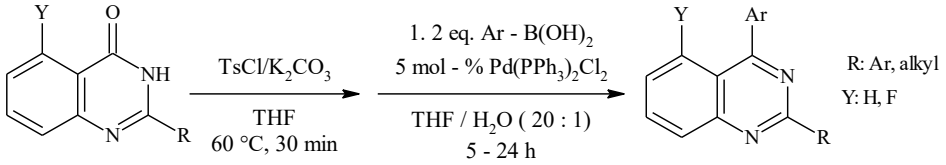
Scheme 20. Utilizing of substituted (2-bromophenyl)methylamines



Scheme 21. Utilizing of Ullmann-type coupling synthesis of 2-substituted quinazolin-4(3*H*)-ones



Scheme 22. Utilizing of 2-aminobenzylamines to synthesis of 2-substituted quinazolin-4(3*H*)-ones



Scheme 23. Synthesis of 4-arylquinazolines

A copper-catalyzed reaction of substituted 2-bromo-benzonitriles with amidines or guanidine yielded 4-amino-quinazoline and 2,4-diaminoquinazoline derivatives (Yang et al., 2010) (Scheme 24).

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 (Wang et al., 2011) (Scheme 25).

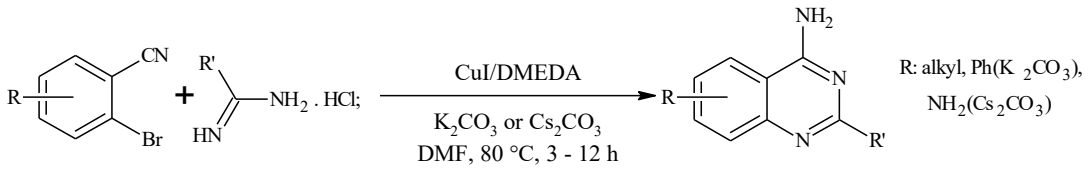
Synthesis of 4-amino-2-aryl(alkyl)quinazolines from readily available *N*-arylamidines and isonitriles via palladium-catalyzed intramolecular aryl C-H amidination by isonitrile insertion (Wang et al., 2011) (Scheme 25).

Microwave-promoted reactions of *O*-phenyl oximes with aldehydes in the presence of $ZnCl_2$ based on convenient free-radical work very well with R: (aryl or alkyl) and heterocyclic aldehydes (Portela-Cubillo et al., 2009) (Scheme 26).

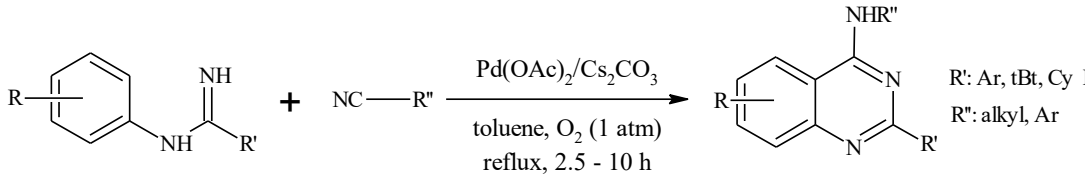
A very fast photochemically induced Fries rearrangement of anilides gave several *o*-amino acylbenzenes that were acylated with a rapid microwave-assisted cyclization to 2,4-disubstituted quinazolines (Ferrini et al., 2007) (Scheme 27).

N -substituted 2,4-diaminoquinazolines products were yields obtained by condensation of a cyanoimidate with an amine followed by reductive cyclization in an iron-HCl system (Yin et al., 2012) (Scheme 28).

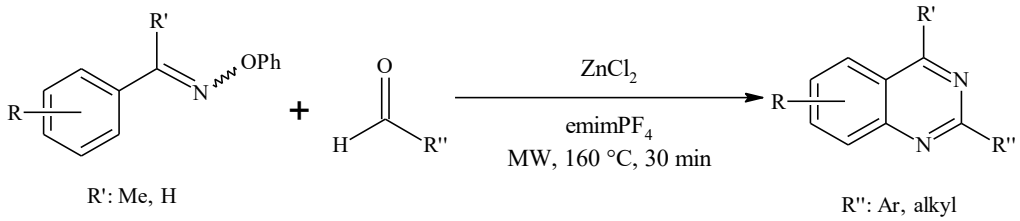
Bergman cyclization involves the synthesis of new 10-membered ring pyrimidine enediynes synthesized in eight steps, respectively. These compounds were compared for their abilities to undergo both thermal and photochemical cleavage of dsDNA under appropriate condition (Choy et al., 2000) (Scheme 29).



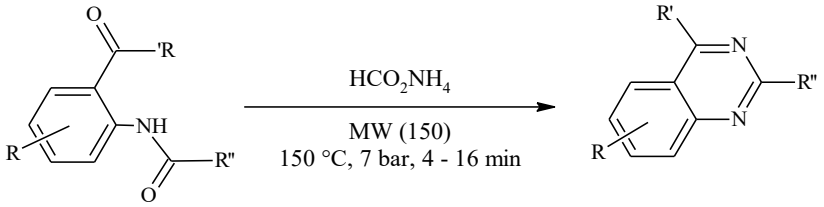
Scheme 24. Utilizing of 2-bromobenzonitriles to synthesis of 2,4-disubstituted quinazolin-4(3*H*)-ones



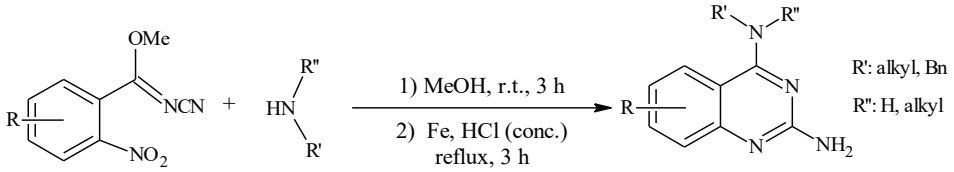
Scheme 25. Synthesis of 4-amino-2-aryl(alkyl)quinazoline



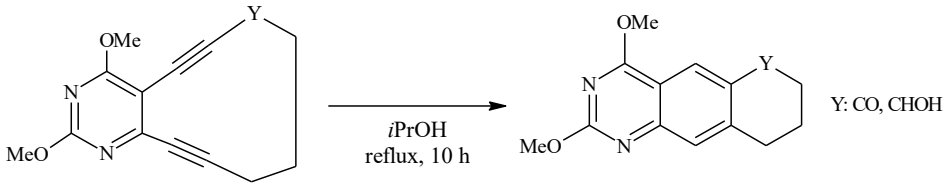
Scheme 26. Utilizing of microwave to synthesis of 2,4-disubstituted-quinazolin-4(3*H*)-ones



Scheme 27. B Fries rearrangement to synthesis of 2,4-disubstituted quinazolin-4(3*H*)-ones

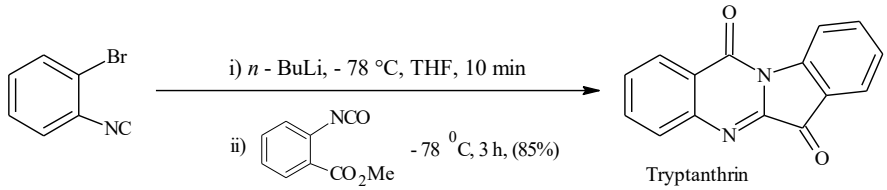


Scheme 28. Synthesis of *N*-substituted-2,4-diaminoquinazolines

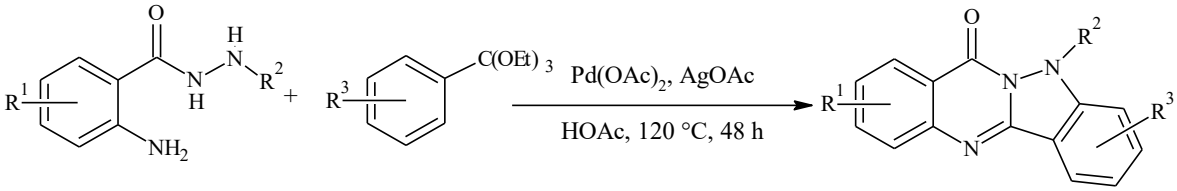


Scheme 29. Bergman cyclization

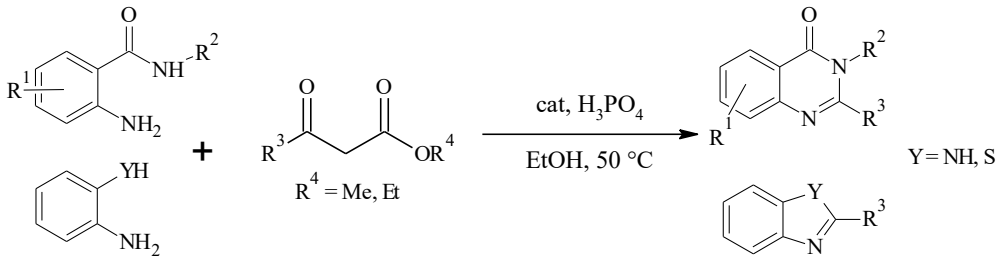
Lygin et al reported one pot synthesis of tryptanthrin from *o*-bromophenylisocyanide and isocyanates (Lygin et al.,2009)(Scheme 30). A palladium-catalyzed seq-uential cyclization/C–H activation cascade reaction of 2-amino-*N′*-arylbenzo hydrazides with triethylorthobenzoates has been developed, providing indazolo[3,2-*b*]quinazolinones (Yang et al.,2015) (Scheme 31). An efficient phosphorous acid-catalyzed cyclocondensation of *β*-ketoesters with *o*-amino benzamides via selective C–C bond cleavage leading to quinazolinones was developed. This reaction gave both 2-alkyl- and 2-aryl-substituted quinazolinones in excellent yields (Dong et al., 2015) (Scheme 32).



Scheme 30. Synthesis of Tryptanthrin



Scheme 31. Synthesis of indazolo[3,2-*b*]quinazolinones



Scheme 32. Phosphorous acid-catalyzedcyclocondensation

2. Conclusion

The presence of substituent at different position(s) of quinazoline or quinazolinone moiety determines its biological activity. The inventions of new methods of their synthesis widen their biological profile.

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