

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

K.M. Darwish* and O.O. Dakhil

Department of Chemistry, Faculty of Science, University of Benghazi, Benghazi, Libya

ARTICLE INFO

Article history:

Received 17 November 2016

Revised 18 April 2017

Accepted 20 April 2017

Available online 18 May 2017

Keywords:

Quinazolines, Quinazolinones, Synthetic Methods, Biological Activities.

* Corresponding author:

E-mail address: kdarwish1962@gmail.com

K.M. Darwish

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.

©2017 University of Benghazi. All rights reserved.

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

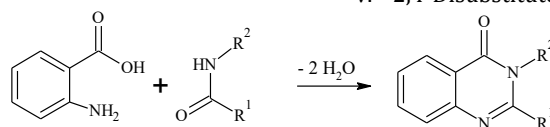
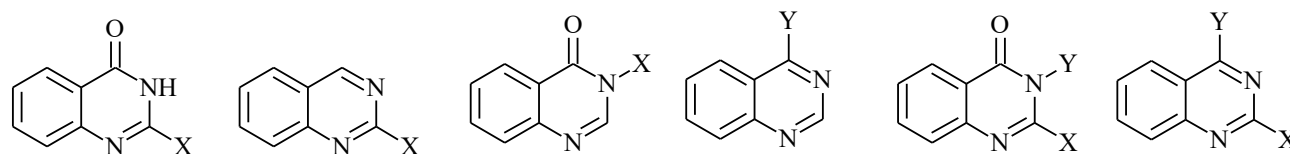
Scheme 1. Synthesis of 4-(3*H*)-quinazolinone

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).

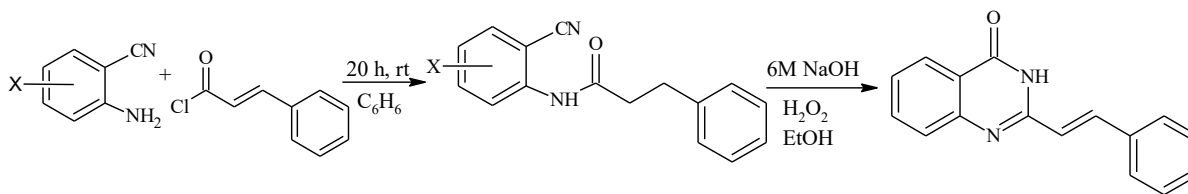
Based on our current review, the syntheses of both quinazolinones and quinazolines can be classified into the following categories according to the substitution patterns of the ring system (Fig. 1):

- 2-Substituted-4(3*H*)-quinazolinones and -quinazolines.
- 3-Substituted-4(3*H*)-quinazolinones.
- 4-Substituted-quinazolines.
- 2,4-Disubstituted quinazolinone.
- 2,4-Disubstituted quinazolines.

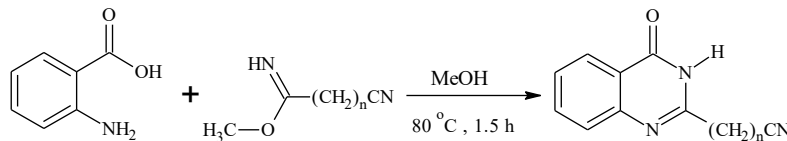
The reaction of anthranilic acid with imidates in methanol at 80 °C affords the desired quinazolinones in good yields (Ried et al., 1963-a, Ried et al., 1962, Ried et al., 1963-b) (Scheme 3). Gruner et al. (2000) developed a novel route to 2-alkylthioquinazolines by heating a suspension of *N*-chloroacetyl anthranilic 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

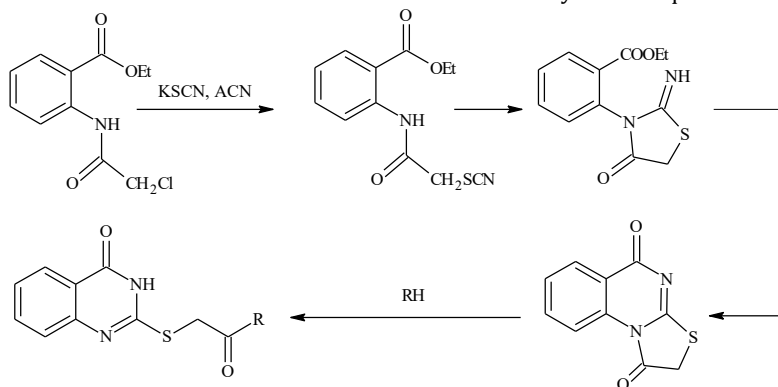
corresponding 4-oxo-3,4-dihydroquinazolines in 43–72% yield (Gruner et al., 2000)(Scheme 4).



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



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

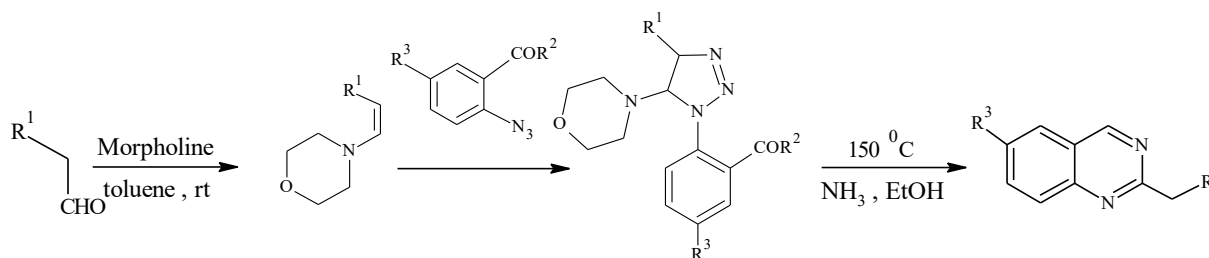


Scheme 4. Synthesis of alkylthio-quinazoline

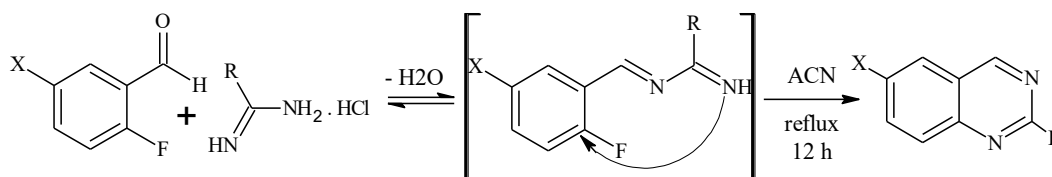
2-Substituted Quinazolines

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). Kotsuki et al.,(1999) developed a condensation of cyano- and nitro activated *o*-fluorobenzaldehydes with amidines to give a variety of quina-

zoline derivatives in good yields. This method involves tandem imine formation with the aldehyde function and an intramolecular 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

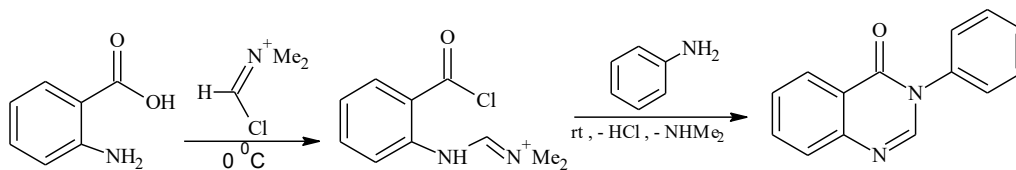
3-Substituted Quinazolinones

A concise and efficient solid-phase synthesis of 2-amino-

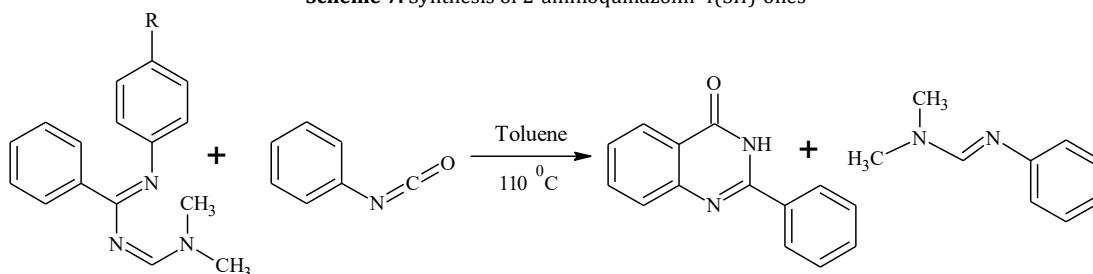
quinazolin-4(3H)-ones was reported by Yang and Kaplau, involving the reaction of polymer-bound isothioureas with

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

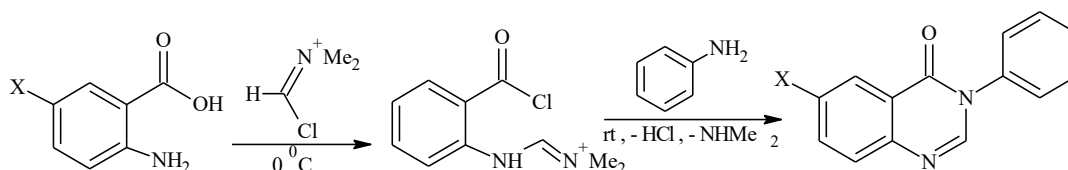
temperature to furnish the desired products in good yields (Croce et al., 1997) (Scheme 8). A novel dimerisation reaction to furnish 3-substituted-4(3H)-quinazolinones in high yield was developed by Perumalet al. by treating 5-substituted-2-amino-benzoic acid derivatives with the Vilsmeier reagent (Majo et al., 1996) (Scheme 9).



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



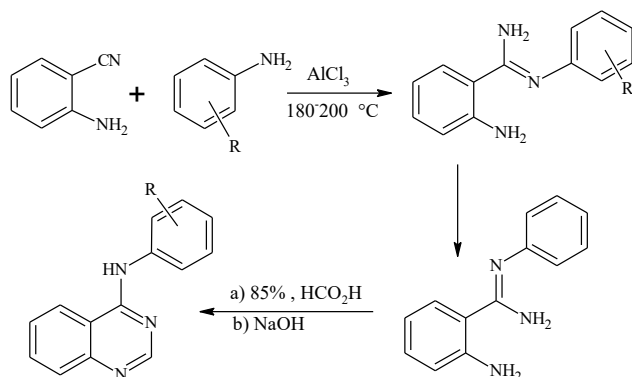
Scheme 8. Synthesis of 2-substituted quinazolinones by Croce et al



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

1.1.2. 4-Substituted Quinazolines

The 2-amino-N-arylbenzamides furnished the 4-arylaminquinazolines 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 (Szczepankiewicz et al., 2000, Szczepankiewicz et al., 1998) (Scheme 10).

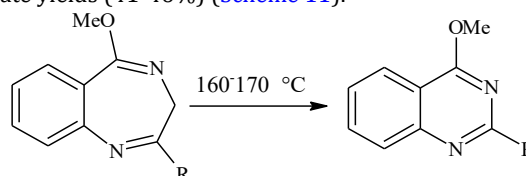


Scheme 10. Synthesis of 4-arylaminquinazolines

2,4-Disubstituted Quinazolines

Kaname et al studied the thermolysis of 5-methoxy- and 5-diethylamino-(3H)-1,4-benzodiazepines to give 4-methoxy- and 4-diethylaminoquinazolines by a ring contraction mechanism (Kaname et al., 1999). On heating 5-methoxy-(3H)-1,4-benzodiazepines in diphenyl ether at 160–170 °C for 6 h, 4-

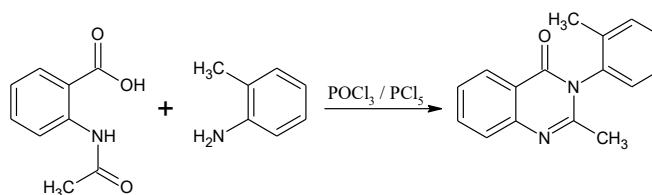
methoxyquinazolines were furnished as the sole products in moderate yields (41–46%) (Scheme 11).



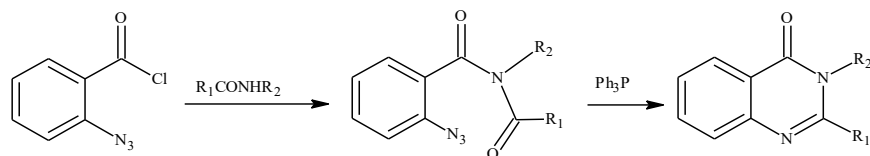
Scheme 11. Synthesis of 4-methoxyquinazolines

1.1.1. 2,3-Disubstituted Quinazolinones

Methaqualone, a sedative hypnotic, was prepared by the fusion of N-acetyl anthranilic acid with o-toluidine using POCl3 or PCl5 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 triphenylphosphine in the course of consecutive Staudinger reaction/intramolecular aza-wittig reaction quantitatively give 2,3-disubstituted-quinazolin-4(3H)ones (Eguchi 2005, Takeuchi et al., 1989a-b) (Scheme 13).



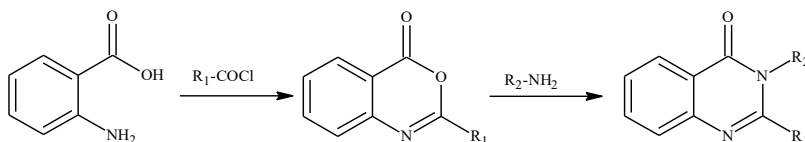
Scheme 12. Synthesis of methaqualone



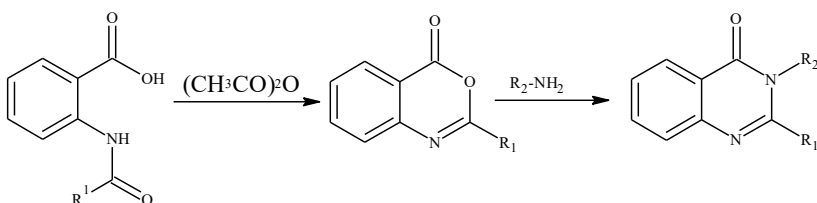
Scheme 13. Synthesis of 2,3-disubstituted quinazolin-4(3H)-ones using amides

Anthranilic acid on reaction with acid chloride also forms benzoxazinone which on reaction with primary amine yield 2,3-disubstituted-quinazolin-4(3H)ones (Acharyulu et al., 2008, Ameta et al., 2006)(Scheme 14). Acetantranil (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 acylantranils 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

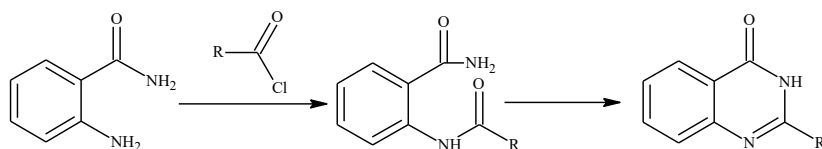
media to give high yield of quinazolin-4(3H)ones (Zhou et al 2004, Patel et al., 2002, Parmar et al., 1968). Reactions of substituted aromatic amine with acetantranil have been extensively studied (Erred et al., 1976, 1977a-b)(Scheme 15). The synthetic methodology commence with the synthesis of anthranil 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(3H)ones (Roy et al., 2006, Witt et al., 2000, Bergman et al., 1990) (Scheme 16).



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



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



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

1.1.1. Miscellaneous Metal-Catalyzed Syntheses of Quinazolines

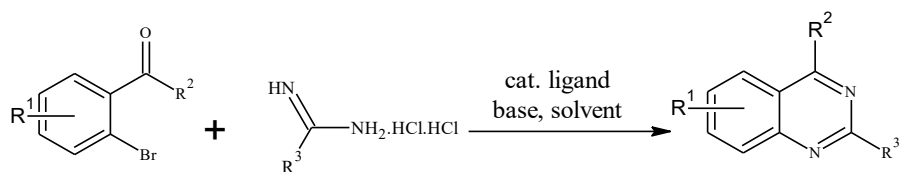
A copper-catalyzed cascade method of coupling reaction of 2-bromobenzaldehyde with acetamidine hydrochloride with optimized conditions has been made (Jiang et al., 2008) (Scheme 17). 2-Arylquinazolines were synthesized from 2-amino-benzophenones and benzylic amines in good yields using ceric ammonium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

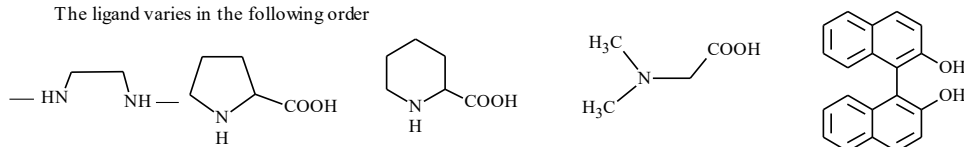
catalyst, and air as the oxidant at 100 °C for 24 h and with DMSO as solvent (Liu et al., 2013) (Scheme 20).

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).

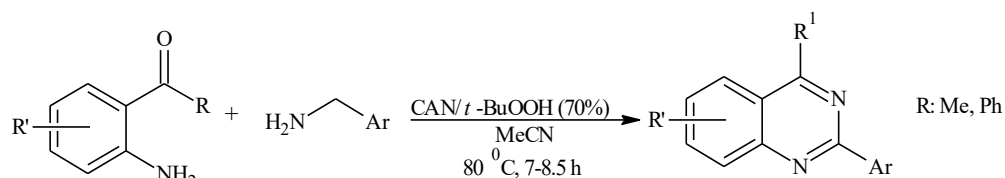


The ligand varies in the following order

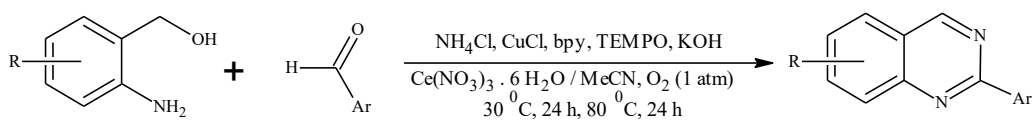


The catalyst is either CuI or CuBr and the base may be CsCO₃ or Na₂CO₃ or K₃PO₄ and the solvent is mostly DMF

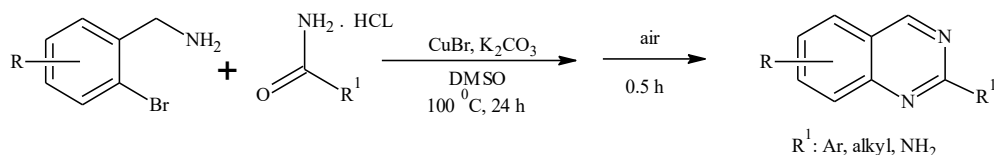
Scheme 17. Copper-catalyzed method



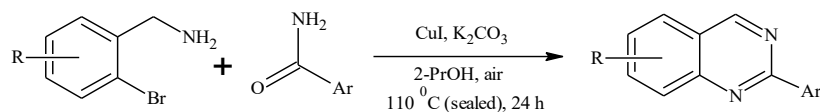
Scheme 18. Synthesis of 2-arylquinazolines from 2-aminobenzophenones



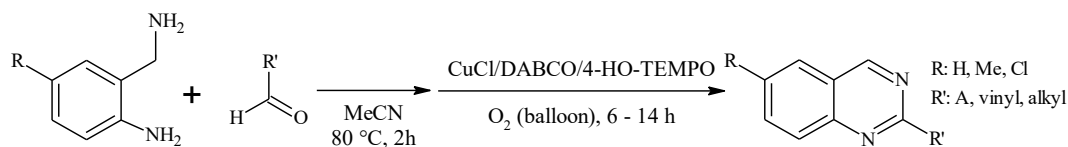
Scheme 19. Cascade copper-catalyzed reaction of (2-aminophenyl)methanol



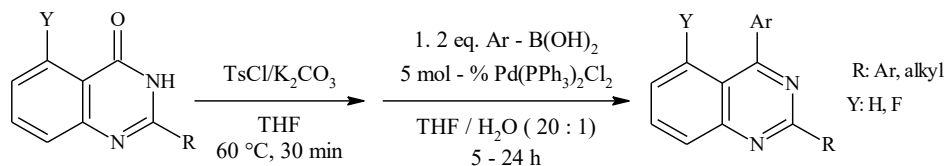
Scheme 20. Utilizing of substituted (2-bromophenyl)methylamines



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



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



Scheme 23. Synthesis of 4-arylquinazolines

A copper-catalyzed reaction of substituted 2-bromobenzonitriles with amidines or guanidine yielded 4-aminoquinazoline 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).

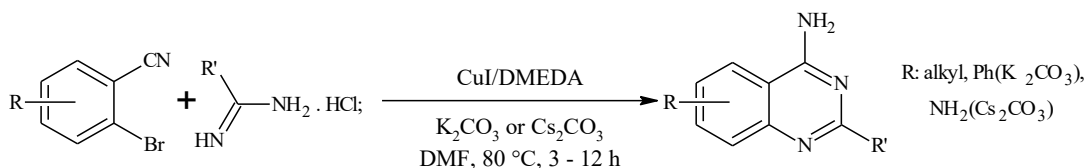
Microwave-promoted reactions of *O*-phenyl oximes with aldehydes in the presence of ZnCl₂ based on convenient free-

radical work very well with R: (aryl or alkyl) and heterocyclic aldehydes (Portela-Cubillo et al., 2009) (Scheme 26).

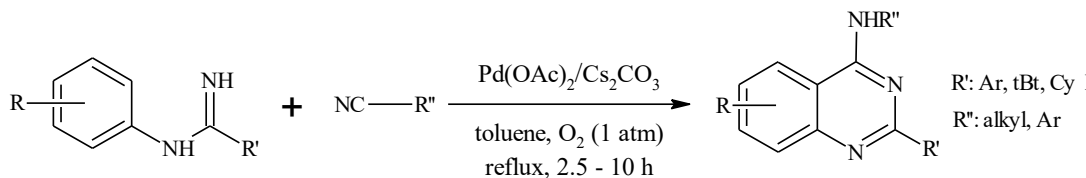
A very fast photochemically induced Fries rearrangement of anilides gave several *o*-amino acylbenzenes that were acylated with a rapid microwave-assisted cyclization to 2,4-disubstituted quinazolines (Ferrini et al., 2007) (Scheme 27).

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

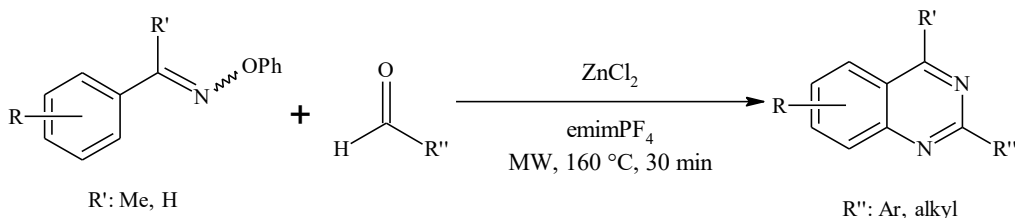
Bergman cyclization involves the synthesis of new 10-membered ring pyrimidine enediynes synthesized in eight steps, respectively. These compounds were compared for their abilities to undergo both thermal and photochemical cleavage of dsDNA under appropriate condition (Choy et al., 2000) (Scheme 29).



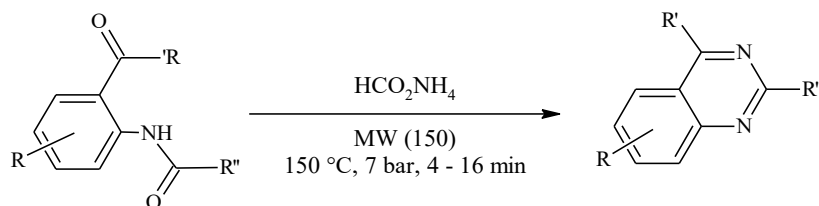
Scheme 24. Utilizing of 2-bromobenzonitriles to synthesis of 2,4-disubstituted quinazolin-4(3H)-ones



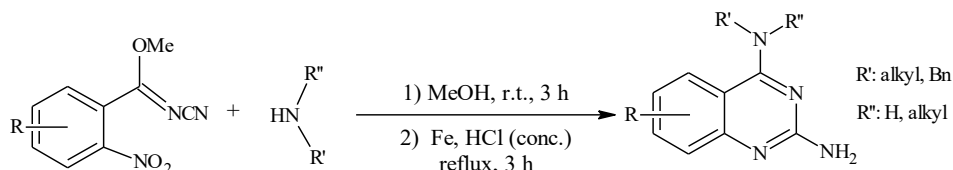
Scheme 25. Synthesis of 4-amino-2-aryl(alkyl)quinazoline



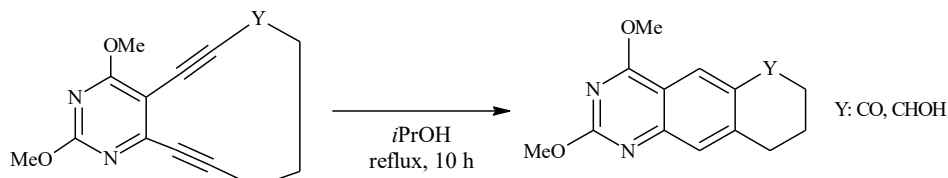
Scheme 26. Utilizing of microwave to synthesis of 2,4-disubstituted-quinazolin-4(3H)-ones



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

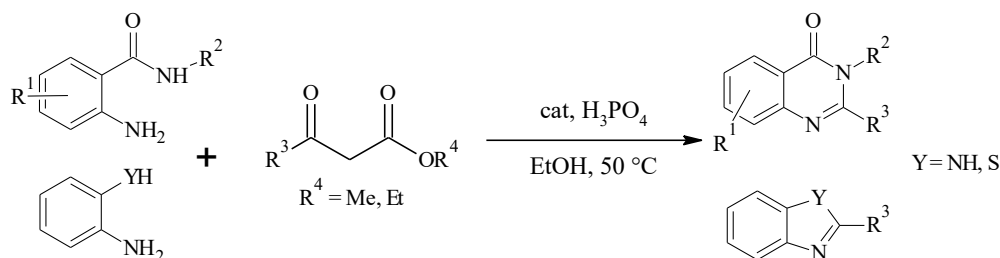
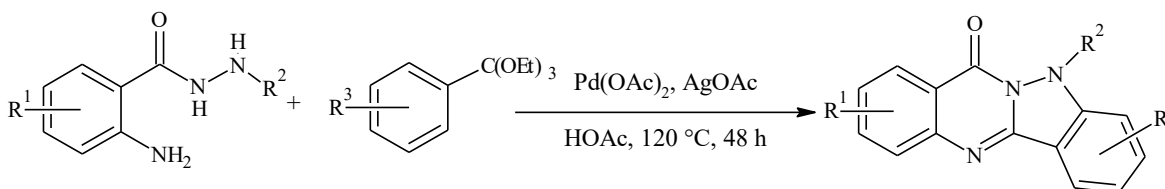
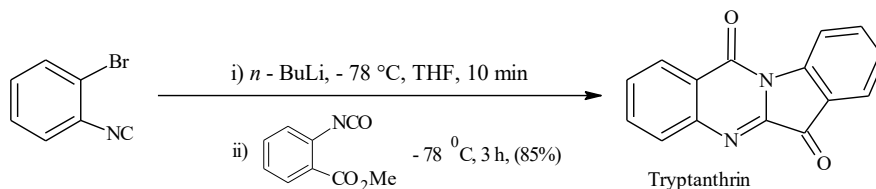


Scheme 28. Synthesis of *N*-substituted-2,4-diaminoquinazolines



Lygin et al reported one pot synthesis of tryptanthrin from *o*-bromophenylisocyanide and isocyanates (Lygin et al.,2009)(Scheme 30). A palladium-catalyzed sequential cyclization/C–H activation cascade reaction of 2-amino-*N*'-arylbenzo hydrazides with triethylortho-benzoates 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).



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.

References

- Abdullah M. A. and Salman A. K. (2011) *Molbank*, 2011, M736. doi:10.3390/M736.
- Acharyulu P.V.R., Dubey P.K., Prasada Reddy P.V.V., Suresh T. (2008) *Arkivoc*, 11, pp. 104.
- Ameta U., Ojha S., Bhambi D. and Talesara G.L. (2006) *Arkivoc*, 13, pp. 83.
- Bergman J. and Brynolf A. (1990) *Tetrahedron*, 46(4), pp. 1295.
- Bogert M. T. and Hand W. F. (1902) *J Am Chem Soc*, 24, pp. 1031.
- Bogert M. T. and Hand W. F. (1903) *J Am Chem Soc*, 25, pp. 935.
- Chen Z, Chen J, Liu M, Ding J, Gao W, Huang X, Wu H. (2013) "Unexpected copper-catalyzed cascade synthesis of quinazoline derivatives", *J. Org. Chem.*, 78, pp. 11342-11348.
- Choy N, Blanco B, Wen J, Krishan A, Russel KC (2000) "Photochemical and thermal bergman cyclization of a pyrimidine enediynol and enediynone", *Org. Lett.*, 2, pp. 3761-3764.
- Croce P. D., Ferracioli R. and La Rosa C. (1997) *Heterocycles*, 45, pp. 1309.
- Eguchi S. (2005) *Arkivoc*, 2, pp. 98.
- Erba E., Pocor D. and Valk M. J. (1999) *J Chem Soc Perkin Trans*, 1, pp. 421.
- Errede L.A. (1976) *J. Org. Chem.*, 41, pp. 1763.
- Errede L.A., McBardy J.J. & Oien H.T. (1977) *J. Org., Chem.*, 42, pp. 656.
- Errede L.A., Oien H.T. & Yarian D.R. (1977) *J. Org. Chem.*, 42, pp. 12.

- Ferrini S, Ponticelli F, Taddei M (2007) "Convenient synthetic approach to 2,4-disubstituted quinazolines", *Org. Lett.*, 9, pp. 69-72.
- Gabriel P. (1903) *BerDtschChemGes*, 36, pp. 800.
- Gruner M., Rehwald M., Eckert K. and Gewald K. (2000) *Heterocycles*, 53, pp. 2363.
- Han B, Yang XL, Wang C, Bai YW, Pan TC, Chen X, Yu W. (2012) "CuCl/DABCO/4-HOTEMPO-Catalyzed Aerobic Oxidative Synthesis of 2-Substituted Quinazolines and 4*H*-3,1-Benzoxazines", *J. Org. Chem.*, 77, pp. 1136-1142.
- Huang C., Fu Y., Fu H., Jiang Y., Zhao Y. (2008) "Highly efficient copper-catalyzed cascade synthesis of quinazoline and quinazolinone derivatives", *Chem. Commun.*, pp. 6333-6335.
- Irwin W. J. and Wibberly D. G. (1965) *J ChemSocChemCommun*, pp. 4240.
- Kaname, M.; Tsuchiya, T., Sashida H (1999) *Heterocycles*, 51, pp. 2407.
- Karnakar K, Shangkar J, Murthy SN, Ramesch K, Nageshwar YVD (2011) "An efficient protocol for the synthesis of 2-phenylquinazolines catalyzed by ceric ammonium nitrate (CAN)", *Synlett*, 4, pp. 1089-1096.
- Kotsuki H., Sakai H., Morimoto H. and Suenaga H. (1999) *Synlett*, 12, pp. 1993.
- Li Z, Dong J, Chen X, Li Q, Zhou Y and Yin S-F (2015) "Metal- and Oxidant-Free Synthesis of Quinazolinones from β -Ketoesters with *o*-Aminobenzamides via Phosphorous Acid-Catalyzed Cyclocondensation and Selective C–C Bond Cleavage", *J. Org. Chem.*, 80, pp. 9392–9400.
- Liu Q, Zhao Y, Fu H, Cheng C. (2013) "Copper-catalyzed sequential *N*-Arylation and aerobic oxidation: Synthesis of Quinazoline Derivatives", *Synlett*, 24, pp. 2089-2094.
- Lygin A. V. and Meijere A. D. (2009) *Org. Lett.*, 11, pp. 389.
- Majo V. J. and Perumal P. T. (1996) *Tetrahedron Lett*, 37, pp. 5015.
- Mattner P.G., Salmond W.G. and Denzer M. (1973) *Fr Pat.*, 2174828.
- Parmar S.S. and Arora R.C. (1968) *Canadian J. Chem.*, 46, pp. 2519.
- Patel V., Patel M.P. and Patel R.G. (2002) *J. Serb. Chem. Soc.*, 67(11), pp. 719.
- Portela-Cubillo F, Scott JS, Walton JC (2009) "Microwave-promoted syntheses of quinazolines and dihydroquinazolines from 2-aminoarylalkanone *o*-phenyl oximes", *J. Org. Chem.*, 74, pp. 4934-4942.
- Qiu G, Huang P, Yang Q, Lu H, Xu J, Deng Z, Zhang M, Peng Y. (2013) "Synthesis of 4-Arylquinazolines by Arylation of Quinazolin-4-ones under Mild Conditions", *Synthesis*, 45, pp. 3131-3136.
- Ried W. and Sinharay A. (1963) *ChemBer*, 96, pp. 3306.
- Ried W. and Stephan W. (1962) *ChemBer*, 95, pp. 3042.
- Ried W. and Stephan W. (1963) *ChemBer*, 96, pp. 1218.
- Roy A.D., Subramanian A. and Roy R. (2006) *J. Org. Chem.*, 71(1), pp. 382.
- Szczepankiewicz W. and Suwinski J. (1998) *Tetrahedron Lett.*, 39, pp. 1785.
- Szczepankiewicz W., Suwinski J. and Bujok R. (2000) *Tetrahedron Lett.*, 56, pp. 9343.
- Takeuchi H. and Eguchi S. (1989) *Tetrahedron Lett.*, 30, pp. 3313.
- Takeuchi H., Hagiwara S. and Eguchi S. (1989) *Tetrahedron*, 45, pp. 6375.
- Taylor E. C., Knopf R. J. and Borrer A. L. J. (1960) *Am ChemSoc*, 82, pp. 3152.
- Wang C, Li S, Liu H, Jiang Y, Fu H. (2010) "Copper-catalyzed synthesis of quinazoline derivatives via ullmann-type coupling and aerobic oxidation", *J. Org. Chem.*, 75, pp. 7936-7938.
- Wang Y, Wang H, Peng J, Zhu Q. (2011) "Palladium-Catalyzed Intramolecular C(sp²)-H Amidination by Isonitrile Insertion Provides Direct Access to 4-Aminoquinazolines from *N*-Aryl amidines", *J. Org. Lett.*, 13, pp. 4596-4599.
- Witt A. and Bergman J. (2000) *Tetrahedron*, 56, pp. 7245.
- Yang R.Y. and Kaplan A. (2000) *Tetrahedron Lett*, 41, pp. 7005–7008.
- Yang W, Qiao R, Chen J, Huang X, Liu M, Gao W, Ding J and Wu H (2015) "Palladium-Catalyzed Cascade Reaction of 2-Amino-*N'*-arylbenzohydrazides with Triethyl Orthobenzoates To Construct Indazolo[3,2-*b*]quinazolinones", *J. Org. Chem.*, 80, pp. 482–489.
- Yang X, Liu H, Qiao R, Jiang Y, Zhao Y. (2010) "Efficient copper-catalyzed synthesis of 4-aminoquinazoline and 2,4-diaminoquinazoline derivatives", *Synlett*, pp. 101-106.
- Yin P, Liu N, Deng YX, Chen Y, Deng Y, He L (2012) "Synthesis of 2,4-diaminoquinazolines and tricyclic quinazolines by cascade reductive cyclization of methyl *n*-cyano-2-nitrobenzimidates", *J. Org. Chem.*, 77, pp. 2649-2658.
- Zentmayer D.T. and Wagner E.C. (1949) *J. Org. Chem.*, 14, pp. 965.
- Zhou Y., Murphy D.E., Sun Z. and Gregor V.E. (2004) *Tetrahedron Lett.*, 45, pp. 8049.