

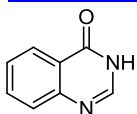
Synthesis of 4-quinazolinones by transition metal-catalyzed processes (microreview)

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4-Quinazolinones are considered as an important class of heterocyclic compounds with various physiological activities and pharmacological utility. In this review, the recent advances in the synthesis of 4-quinazolinone derivatives are highlighted. Only the methods using transition metal catalysis published in 2014–2017 are summarized.

Introduction

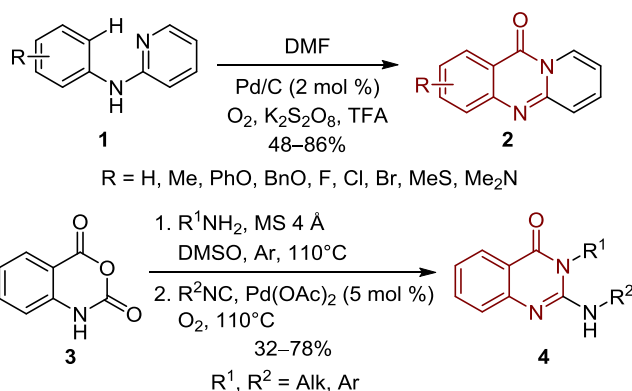
4-Quinazolinones are more common than their structural isomers 2-quinazolinones. 4-Quinazolinone derivatives are significant class of nitrogen-rich heterocyclic compounds, as this moiety is present in a variety of bioactive natural products, synthetic drugs, agrochemicals, and pharma-

ceuticals.¹ Due to their extensive range of applications, considerable efforts have been made to the expansion of synthetic approaches. This microreview summarizes the methods that have not been covered in a recent comprehensive review.²

Pd-catalyzed routes

There are some examples of transition metal-catalyzed approaches toward the synthesis of 4-quinazolinones, including the use of palladium catalysis.³ A representative example is the Pd/C-catalyzed carbonylative cyclization of *N*-arylpyridin-2-amine derivatives **1** into pyrido[2,1-*b*]quinazolin-1(1H)-ones **2** via C–H activation in the presence of DMF as the CO source.⁴

2-Amino-4-quinazolinones **4** can be obtained from isatoic anhydride (**3**), amines, and isonitriles in a one-pot aerobic oxidative palladium-catalyzed reaction. Isatoic anhydride (**3**) with amines produces anthranilic acid amides which undergo palladium(II)-catalyzed isonitrile insertion leading to the final product **4**.⁵



Vaezeh Fathi Vavsari was born in Iran, in 1983. She received her BSc degree in Applied Chemistry from the Ferdowsi University of Mashhad, Iran, in 2009, and MSc degree in Organic Chemistry at the Khaje Nasir Toosi University of Technology, Tehran, Iran, in 2013, under the supervision of Prof. Saeed Balalaie. She obtained her PhD degree in organic chemistry at the Alzahra University under the supervision of Prof. Ghodsi Mohammadi Ziarani. Her research field is organic synthesis by use of amino acids and hydrazides in the presence of modified nanostructure silicas as catalysts.



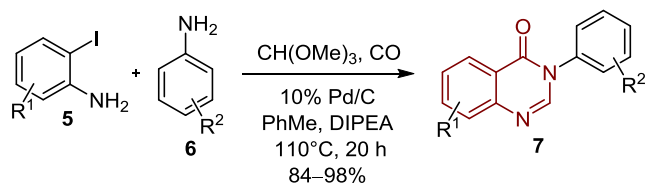
Ghodsi Mohammadi Ziarani was born in Iran, in 1964. She received her BSc degree in Chemistry from the Teacher Training University (Kharazmi University), Tehran, Iran, in 1987, and MSc degree in Organic Chemistry from the same university, under the supervision of Professors Jafar Asgarin and Mohammad Ali Bigdeli in 1991. She obtained her PhD degree in asymmetric synthesis (biotransformation) from the Laval University, Canada, under the supervision of Professor Chenevert, in 2000. She is currently a full Professor in the Alzahra University. Her research interests include organic, heterocyclic, and asymmetric synthesis, natural product synthesis, as well as applications of nanoheterogeneous catalysts in multicomponent reactions.

Pd-catalyzed routes (continued)

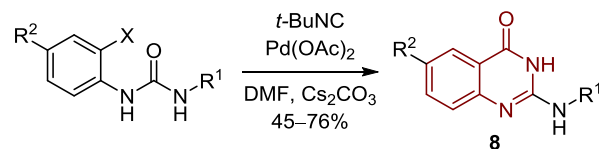
Another interesting example is the carbonylation of 2-iodoanilines **5** by heterogeneous palladium catalysis followed by amidation with amines **6** and ring closure with trimethyl orthoformate, which results in quinazolin-4(3*H*)-ones **7** in excellent yields.⁶

In order to synthesize biologically important molecules in a straightforward and atom-economical fashion, Sharma and Jain developed a ligand-free Pd-catalyzed reaction for the synthesis of phenyl(alkyl)amino-substituted quinazolinone derivatives **8** via isocyanide insertion/rearrangement approach in the presence of DMF and Cs₂CO₃.⁷

Recently, Wu and coworkers reported their new findings on using the carbonyl group of DMF as the CO source for Pd-catalyzed synthesis of 11*H*-pyrido[2,1-*b*]quinazolin-11-ones through C–H bond activation and annulation. The methodology worked well for both electron-rich and electron-poor substrates and gave the desired products in good to excellent yields.⁸



R¹ = F, Cl, CN; R² = OMe, SMe, Cl, Br, F, CF₃, COMe, Me, OH



R¹ = Alk, Ar; R² = H, Cl; X = I, Br

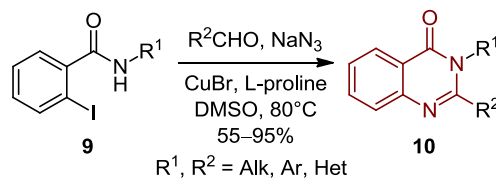
Cu-catalyzed routes

Li and coworkers have developed a copper-catalyzed reaction of 2-iodobenzamides **9**, aldehydes, and sodium azide for the efficient synthesis of quinazolin-4(3*H*)-ones **10** in moderate to good yields. The authors have suggested an integrated consecutive process which consists of a copper-catalyzed S_NAr reaction, reduction, cyclization, and oxidation sequence.⁹ A variety of aromatic aldehydes bearing electron-neutral or electron-donating groups on the aromatic ring, as well as sterically hindered (*ortho*-substituted) aldehydes could be used in this reaction, likewise also thiophene-2-carbaldehyde, furan-2-carbaldehyde, picolinaldehyde, and alkylaldehydes, including formaldehyde and *n*-butylaldehyde.

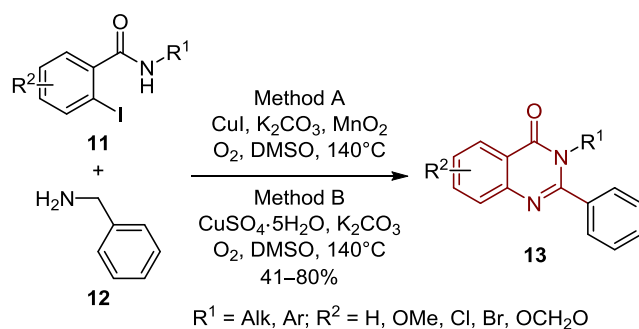
The synthesis of quinazolinone derivatives **13** is also achieved from *N*-substituted 2-iodobenzamide derivatives **11** and benzylamine (**12**) through a one-pot copper-catalyzed reaction. In this reaction, the amine component is *N*-arylated with 2-iodobenzamide derivatives through the Ullman coupling, followed by an intramolecular C–H amidation in the presence of copper catalysts.¹⁰

In a recent study, Zhang and coworkers investigate a simple and sustainable synthesis of diversely substituted pyrazoloquinazolinones **17** via copper-catalyzed cascade reactions of 2-bromobenzoates **14** with 5-aminopyrazoles **15**. Using similar strategy, [1,2,4]triazolo[1,5-*a*]quinazolin-5(4*H*)-one (**18**) could be obtained from the reaction of 2-bromobenzoate **14** with 5-amino-1*H*-1,2,4-triazole (**16**).¹¹

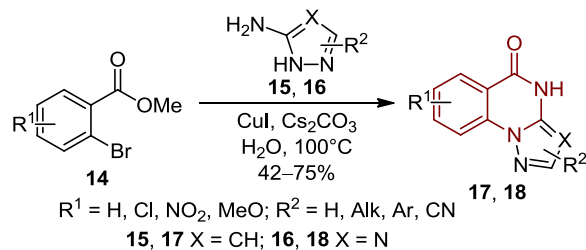
Copper(I)-catalyzed coupling reactions of 2-halobenzoic acids **19** with amidines **20** in the presence of a commercially available surfactant TPGS-750-M produced



R¹, R² = Alk, Ar, Het



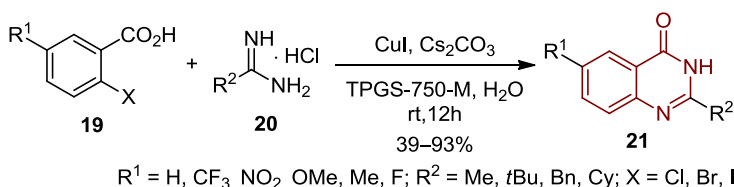
R¹ = Alk, Ar; R² = H, OMe, Cl, Br, OCH₂O



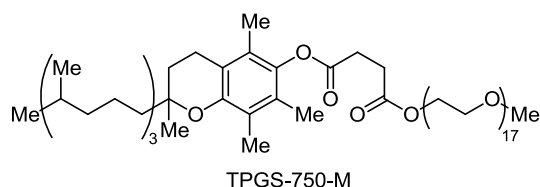
R¹ = H, Cl, NO₂, MeO; R² = H, Alk, Ar, CN

15, **17** X = CH; **16**, **18** X = N

the corresponding quinazolinone derivatives **21** in good to excellent yields at room temperature. In addition, the reaction medium was recycled and recovered.¹²

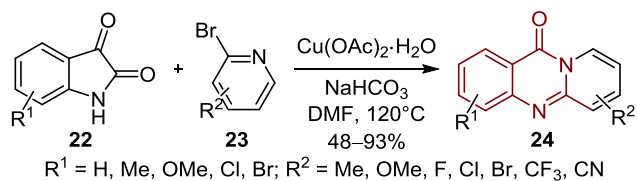


R¹ = H, CF₃, NO₂, OMe, Me, F; R² = Me, *t*Bu, Bn, Cy; X = Cl, Br, I

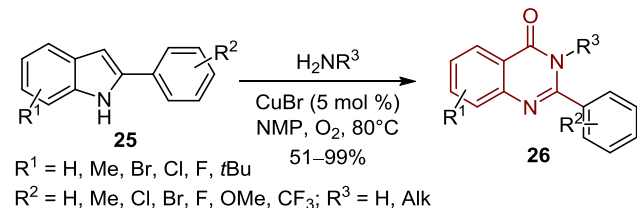


Cu-catalyzed routes (continued)

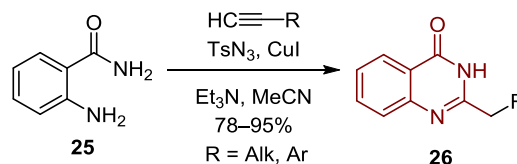
A simple and efficient synthesis of 11*H*-pyrido[2,1-*b*]-quinazolin-11-ones **24** by copper(II) acetate-catalyzed reaction of easily available substituted isatins **22** and 2-bromopyridine derivatives **23** proceeds in moderate to high yields. The reaction involves C–N and C–C bond cleavage and formation of two C–N bonds in a one-pot procedure.¹³



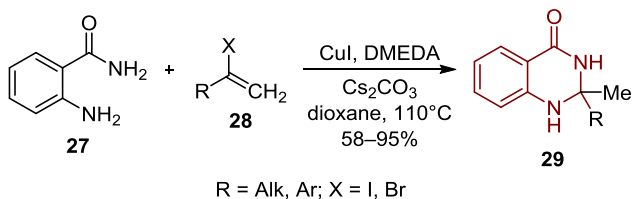
A simple and efficient copper-catalyzed reaction for the construction of quinazolinones **26** starting from 2-arylindoles **25** was developed. It involves CuBr-catalyzed aerobic Baeyer–Villiger oxidation of indoles to the intermediate 4*H*-3,1-benzoxazin-4-ones which undergo cyclization with ammonia or amines.¹⁴



Mulakayala and coworkers have reported the synthesis of substituted quinazolin-4(3*H*)-ones **26** by copper iodide-catalyzed one-pot reaction of anthranilamide **25**, various terminal alkynes, and tosyl azide. The reactions proceeded smoothly with all the alkynes subjected to this.¹⁵

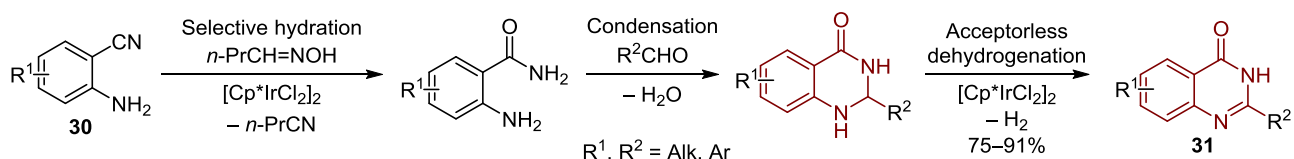


The reaction of 2-aminobenzamides **27** and vinyl halides **28** with the aid of CuI as the catalyst affording 2,2-disubstituted quinazolinone derivatives **29** was reported by Ogawa and coworkers.¹⁶ To understand the reaction pathway, the authors conducted the copper-catalyzed reaction of vinyl iodides with aniline or benzamide independently. The coupling product with aniline was not obtained and the coupling product with benzamide was detected in 34% yield by HPLC.¹⁶

**Ir-catalyzed routes**

A one-pot selective hydration/condensation/acceptorless dehydrogenation process was reported for an efficient synthesis of quinazolinones **31** from *o*-aminobenzonitriles **30** in the presence of [Cp*IrCl₂]₂ (Cp* = pentamethylcyclopentadienyl) catalyst. The selected nitriles undergo iridium-catalyzed hydration with *n*-butylaldoxime as water

surrogate. Further condensation and dehydrogenation provides the target products **31**.¹⁷ Quinazolinones **31** (R² = H) were also obtained from compounds **30** and MeOH with [Cp*Ir(2,2'-bpyO)(H₂O)] (2,2'-bpyO = 2,2'-bipyridine-6,6'-(1*H*,1'*H*)-dione) as catalyst.¹⁸

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