



Novel one pot synthesis of substituted quinazolin-4(3*H*)-ones and pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones using copper iodide, azides and terminal alkynes



V. Srishyalam^a, N. Devanna^a, M.V. Basaveswara Rao^b, Naveen Mulakayala^{c,*}

^a Department of Chemistry, Jawaharlal Nehru Technological University Anantapur, Ananthapuramu, Andhra Pradesh, India

^b Department of Chemistry, Krishna University, Machilipatnam 521 00, India

^c Clearsynth Labs Ltd, Plot No-177, IDA Mallapur, Nacharam, Hyderabad 500076, India

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ABSTRACT

A simple and highly efficient copper iodide catalyzed one-pot synthesis of 2-substituted quinazolin-4(3*H*)-ones have been developed from anthranilamide, terminal alkynes and azides. A wide variety of alkynes were screened to understand the scope of this methodology. This method has been extended for the synthesis of 5-substituted pyrazolo[4,3-*d*]pyrimidin-7(6*H*)-ones which are having potential applications in medicinal chemistry.

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Introduction

4(3*H*)-Quinazolinones are an important class of fused heterocycles, which have drawn great importance due to their biological importance. Quinazolinone is an important scaffold found in about 200 naturally occurring alkaloids isolated till to day from a number of families of the plant kingdom, from animals and from microorganisms (Fig. 1). For example, 2-methyl-4(3*H*)-quinazolinone (1) was isolated from culture of the microorganism *Bacillus cereus*,¹ Pegamine (2), an alkaloid isolated from *Peganum harmala*, exhibits cytotoxic properties.² vasicinone (3) is a pyrrolo[2,1-*b*]quinazoline alkaloid, isolated from the aerial parts of *Adhatoda* (*Justicia adhatoda*), a plant used extensively in indigenous medicine for treating colds, coughs, bronchitis, and asthma.³ Luotonine A (4) was isolated from a Chinese plant named *Luo-Tuo-Hao* (*Peganum nigellastrum*) is a human DNA topoisomerase I inhibitor and displays cytotoxicity toward the murine leukemia P388 cell line (IC₅₀ = 1.8 μg/ml).⁴ Rutaecarpine (5) is the major alkaloid component isolated from dried fruits of *Evodia rutaecarpa*, a Chinese herbal drug used extensively as a remedy for headache, cholera, dysentery and worm infections.⁵ Bouchardatine (6) isolated from *Bouchardatia neurococca*⁶ (Fig. 1).

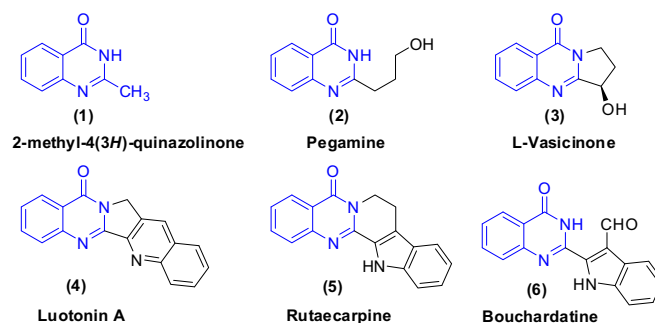


Fig. 1. Naturally occurring 4(3*H*)-quinazolinone alkaloids.

Quinazolinone derivatives have attracted the synthetic community due to their broad spectrum of biological and pharmaceutical activities such as anti-inflammatory,⁷ anticancer,⁸ anti-malarial,⁹ anti-diabetic,¹⁰ anti-tumor,¹¹ anti-microbial,¹² anti-convulsant,¹³ anti-viral,¹⁴ anti-hypertensive,¹⁵ cholinesterase inhibition,¹⁶ epidermal growth factor (EGFR) receptors of tyrosine kinase,¹⁷ ligands for benzodiazepine and GABA receptors in central nervous system,¹⁸ and several others.

Some synthetic quinazolinones such as raltitrexed (for the first-line palliative treatment of advanced colorectal cancer),

* Corresponding author.

E-mail address: naveen071280@gmail.com (N. Mulakayala).

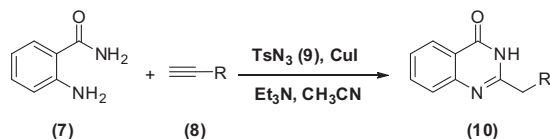
afloqualone (as a muscle relaxant) ispinesib, and tempostatin are already in the market or are in clinical trials.¹⁹

The most common synthetic methods to synthesize quinazolinone derivatives utilize 2-aminobenzoic acid or its derivatives, 2-halobenzoic acids (or) benzamides, 2-aminobenzamide, 2-aminobenzonitrile and isatoic anhydride as suitable precursors. While the reported methods are important in varying degree, some methods are still experience restrictions like poor or inconsistent yields, expensive and environmentally toxic catalysts, long reaction time, substrate tolerance and tedious work up procedures. Hence, a easier and high yielding method towards the synthesis of quinazolinones is much desirable.

As a part of our ongoing research towards the development of new methodologies for the synthesis of biologically important heterocyclic compounds²⁰ we want to study the novel method for the synthesis of 2-substituted quinazolinones. Recently, Ketenimine, has attracted considerable attention due to its high reactivity, easiness to form, and wide scope of substrates tolerance. Herein we report a simple, scalable and straightforward copper catalyzed method for the synthesis of quinazolin-4(1*H*)-ones (10) (Scheme 1) by a one-pot three-component reaction of 2-aminobenzamide (7), Azides (9) and terminal alkynes (8).

Initially, we examined one-pot, three-component condensation reaction of 2-aminobenzamide (7), phenyl acetylene (8a) and *p*-toluenesulfonyl azide (9) as the model substrates by using copper iodide (10 mol%) as catalyst in THF solvent (Table 1, entry 1) and triethylamine as a base. To our delight, the corresponding quinazolin-4(3*H*)-one (10a) derivative was obtained in 60% yield after 24 h at room temperature. Encouraged by this result, we further carried out the optimization experiments with different solvents and different copper catalysts as shown in Table 1.

As shown in the Table 1, different solvents, including THF, 1,4-dioxane, CH₂Cl₂ and DMF were screened but product formation was considerably lower than that obtained by using acetonitrile



Scheme 1. Copper catalyzed one pot synthesis of 2-substituted quinazolin-4(3*H*)-one.

Table 1
Optimization of catalyst and solvents for the preparation of quinazolin-4(3*H*)-one.^a

Entry	Catalyst	Solvent	Yield (%) ^b
1	CuI	CH ₃ CN	65
2	CuI	THF	41
3	CuI	1,4-Dioxane	49
4	CuI	CH ₂ Cl ₂	10
5	CuI	DMF	58
6	CuBr	CH ₃ CN	37
7	CuCl	CH ₃ CN	31

^a Reaction conditions: All the reaction were carried out 2-aminobenzamide (1 mmol), phenylacetylene (1.1 mmol), tosylazide (1.1 mmol), triethylamine (1 mmol) and solvent (10 ml) at room temperatures.

^b Isolated yield.

Table 2
Optimization of bases and catalyst loading for the synthesis of 2-substituted quinazolin-4(3*H*)-one.^a

Entry	Catalyst	Mol%	Base (eq.)	Time (h)	Yield (%) ^b
1	CuI	10	DIPEA (1.0)	24	29
2	CuI	10	K ₂ CO ₃ (1.0)	24	10
3	CuI	10	Et ₃ N (1.0)	12	65
4	CuI	10	Et ₃ N (1.0)	24	81
5	CuI	10	Et ₃ N (2.0)	12	90
6	CuI	10	Et ₃ N (3.0)	12	91
7	CuI	10	Et ₃ N (4.0)	12	87
8	CuI	5	Et ₃ N (2.0)	12	68
9	CuI	20	Et ₃ N (2.0)	12	87
10	CuI	50	Et ₃ N (2.0)	12	74

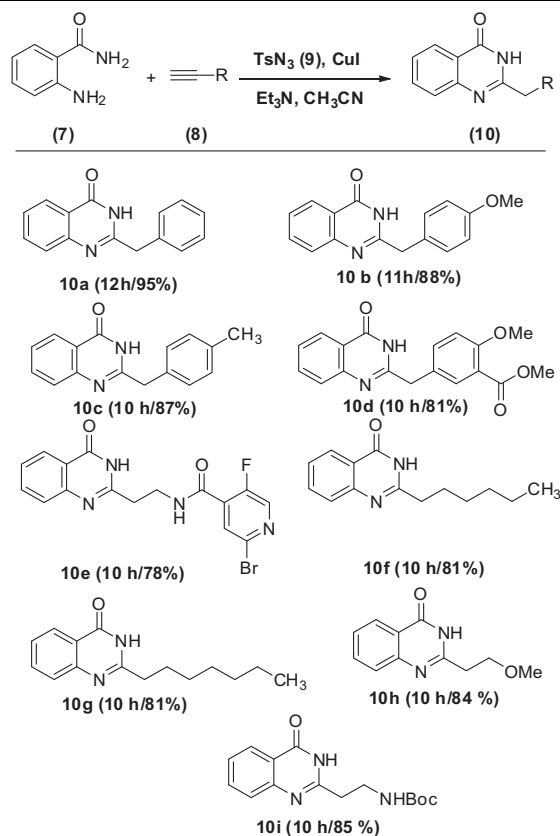
^a Reaction conditions: All the reaction were carried out 2-aminobenzamide (1 mmol), phenylacetylene (1.1 mmol), tosylazide (1.1 mmol) and acetonitrile (10 ml) at room temperatures.

^b Isolated yields.

(entry 1). Further experiments were performed using copper bromide (entry 6) and copper chloride (entry 7) in acetonitrile gave lesser yields compared with copper iodide. Further we carried out optimization of bases and catalyst loading and the results are tabulated in Table 2.

Different bases were screened to optimize the reaction conditions mainly *N,N*-Diisopropylethylamine (DIPEA), potassium carbonate (K₂CO₃) and triethylamine (TEA). In all the above bases DIPEA and K₂CO₃ were produced less yields than triethylamine (Table 2). The influence of base equivalents were also studied

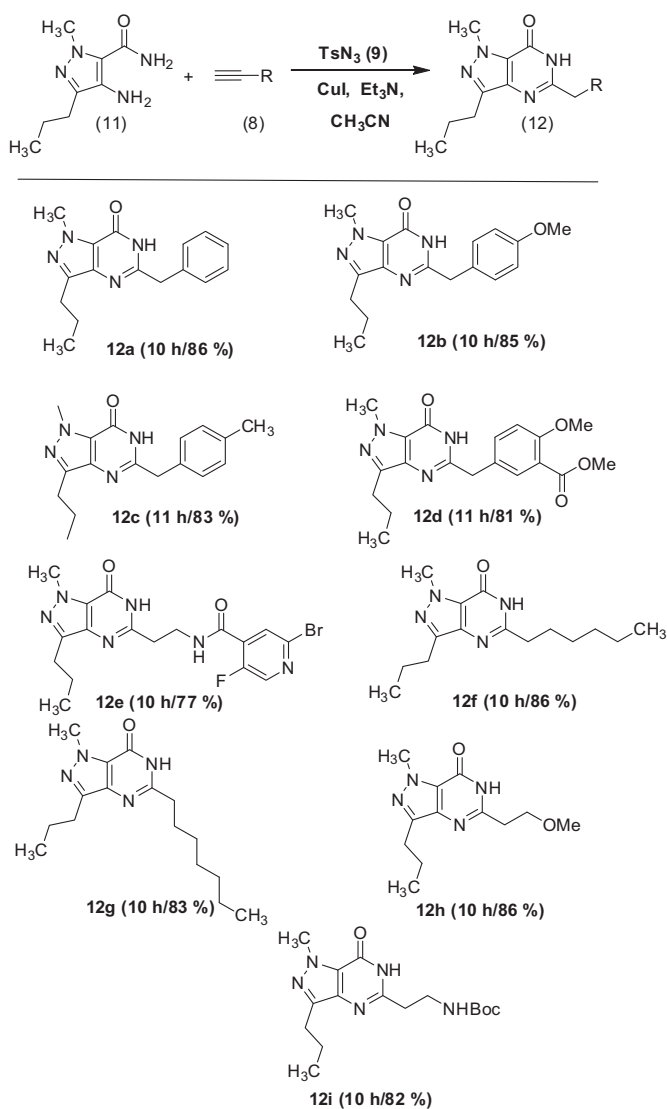
Table 3
Synthesis of 2-substituted quinazolin-4(3*H*)-one.



^aReaction conditions: 2-aminobenzamide (2.0 mmol), terminal alkyne (2.0 mmol), *p*-tolylsulfonyl azide (2.0 mmol), CuI (10 mol%), Et₃N (4.0 mmol), and CH₃CN (10 ml).

^bIsolated yields.

Table 4
Copper iodide-catalyzed synthesis of pyrazolo[4,3-*d*] pyrimidin-7(6*H*)-ones.



^aReaction conditions: 4-amino-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide, **11** (2.0 mmol), terminal alkyne (2.0 mmol), *p*-tolylsulfonamide (2.0 mmol), CuI (10 mol%), Et₃N (4.0 mmol), CH₃CN (10 ml).

^bIsolated yields.

further. When the reaction was performed with 2 eq. of triethylamine gave clean conversion after 12 h with 90% isolated yield. Increasing the catalyst loading from 10 mol% to 20 mol% no significant yield improvement observed. However with increasing catalyst loading from 10 mol% to 50 mol%, also decreasing catalyst loading from 10 mol% to 5 mol% significant yield drop observed.

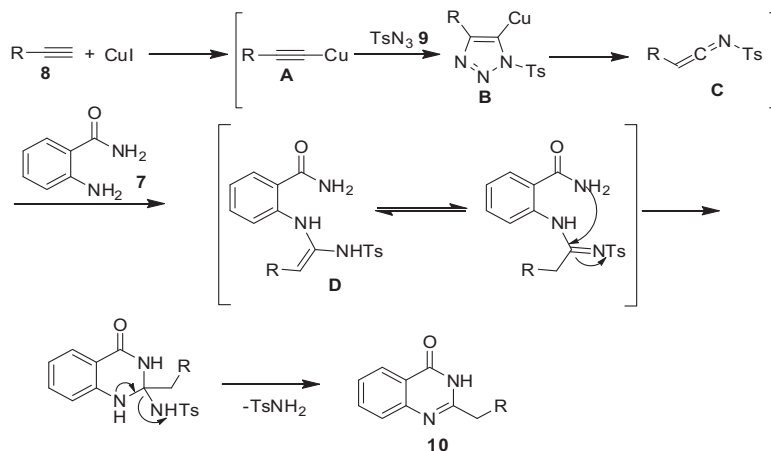
This observation encouraged us to extend the scope and generality of this methodology. A wide variety of terminal alkynes were evaluated using the optimized reaction conditions, and the results are tabulated in Table 3. The reactions were proceeded smoothly and all the alkynes participated well in the reaction. The aromatic alkynes participated well in the reaction affording the corresponding products in high yields (Table 3, entries 1–4). Hetero aromatic acetylenes (entry 5) and aliphatic acetylenes (entry 6–8) also readily participated giving desired products in good yields. More importantly, carbamate functional group (entry 9) also tolerated in the reaction conditions giving the corresponding quinazolinone in 85% yield.

After successful synthesis of 2-substituted quinazolinone 4-(3*H*)-one **10** we want to use this methodology on 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide **11** which can be used as 2-aminocarboxamide source. When 4-amino-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide (**11**), reacted with a mixture of terminal alkynes (**8**) tosyl azide (**9**), TEA in acetonitrile using copper iodide as catalyst afforded corresponding pyrazolo [4,3-*d*] pyrimidin-7(6*H*)-ones (**12**) in good to excellent isolated yields.

Based on the results summarized in Table 4 it was evident that the cascade reaction was proceeded well to give the desired product **12** in good to excellent yields using terminal alkynes. All the synthesized compounds were well characterized by spectral data (NMR and MS).

A plausible mechanism for the formation of substituted quinazolinone 4-(3*H*)-one is illustrated in Scheme 2. Based on previous reports, the copper acetylide **A**, formed from alkyne **8** and copper (I) iodide, undergoes a 1,3-dipolar cycloaddition with azide **9** to give triazole derivative **B**. This intermediate is converted into ketenimide **C**, which is attacked by amine **7** to afford intermediate **D**. This intermediate upon intramolecular cyclization afforded the final product **10**.

In conclusion, we have developed an efficient copper iodide catalyzed one-pot method for the synthesis of 2-substituted 4(3*H*)-quinazolinones from 2-aminobenzamide, azide and various alkynes using copper iodide.²¹ The reaction proceeds under mild conditions, a wide range of substrates fit for the process to afford the corresponding 2-substituted 4(3*H*)-quinazolinones in moderate to good yields. This method was used for the synthesis of



Scheme 2. Plausible reaction mechanism for the formation of 2-substituted quinazolinone 4-(3*H*)-one.

5-substituted pyrazolo[4,3-d]pyrimidin-7(6H)-ones which can be used as important cores in medicinal chemistry.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2017.06.026>.

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21. **General procedure for synthesis of 2-aryl quinazolinones and 5-substituted pyrazolo[4,3-d]pyrimidine-7-one:** To a solution of 2-aminobenzamide (1.470 mmol, 1.0 eq.) was added to a solution of Terminal Alkyne (1.470 mmol, 1.0 eq.), Tosyl Azide, (1.470 mmol, 1.0 eq.), CuI (0.147 mmol, 0.1 eq.), triethylamine (2.941 mmol, 2.0 eq.), in acetonitrile (10 ml) under N₂ atmosphere. The mixture was stirred at room temperature for 12 h. After completion of the reaction (as indicated by TLC) the reaction mixture was poured into water (25 ml) and extracted with ethyl acetate (2 × 25 ml), dried over Na₂SO₄, concentrated under vacuum to get crude compound which was purified by column chromatography using a mixture of petroleum ether: ethyl acetate to give the desired product as white solid.