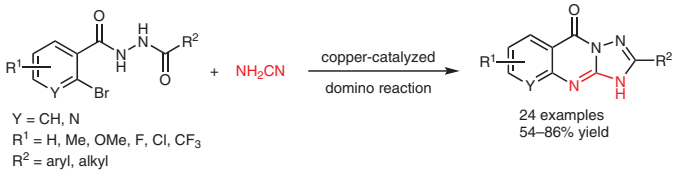
Synlett Z. Lou et al. Letter

Copper-Catalyzed Cascade Synthesis of [1,2,4]-Triazoloquinazolinones

Zhenbang Lou[a,b]
Ningning Man[b]
Haijun Yang[b]
Changjin Zhu[a]
Hua Fu*[a,b]

[a] School of Chemistry and Chemical Engineering, Beijing Institute of Technology, Beijing 100081, P. R. of China
fuhua@mail.tsinghua.edu.cn
[b] Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, P. R. of China



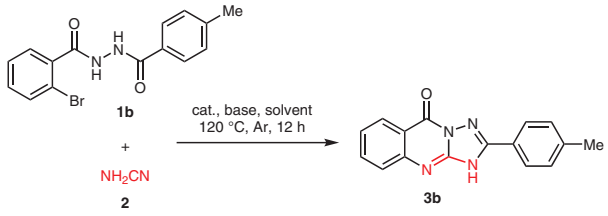
Received: 04.02.2018
Accepted after revision: 12.03.2018
Published online: 20.04.2018
DOI: 10.1055/s-0036-1591565; Art ID: st-2018-k0077-l

Abstract An efficient and practical method for the synthesis of 1,2,4-triazolo[5,1-*b*]quinazolin-9(3*H*)-ones has been developed via the copper-catalyzed domino reactions of readily available substituted *N*′-acetyl-2-bromobenzohydrazides with cyanamide. The protocol uses inexpensive CuI as the catalyst, and no other ligand or additive was required. The target products were prepared in good to excellent yields with tolerance of various functional groups.

Key words copper, domino reactions, [1,2,4]-triazoloquinazolinones, cyanamide, synthetic method

N-Heterocycles are widely found in natural products, biologically and pharmaceutically active molecules,[1] and they are privileged motifs in drug discovery.[2] Quinazolinones constitute an important class of N-heterocyclic compounds, and they exhibit a wide range of biological and pharmaceutical activities such as antimicrobial,[3] antifungal,[4] anti-inflammatory,[5] anticancer[6] and AMPA receptor antagonistic activities.[7] Similarly, N-heterocycles with the 1,2,4-triazole unit show diverse biological functions. For example, they are used as bactericidal, fungicidal, antitumor, anti-inflammatory and insecticidal agents.[8] N-Fused compounds of 1,2,4-triazole and quinazolinone motifs, [1,2,4]-triazoloquinazolinones, have been reported to own excellent antifungal, antirheumatic and antihistaminic activities.[9] To the best of our knowledge, the most common methods for the synthesis of this kind of compounds are cyclization of 3-amino-2-arylaminoquinazolin-4(3*H*)-ones with acyl chlorides, carboxylic acids or aldehydes.[10] However, it is difficult to get the starting materials, 3-amino-2-arylaminoquinazolin-4(3*H*)-ones. In 2004, Ding and co-workers developed the efficient synthesis of 1,2,4-triazolo[5,1-

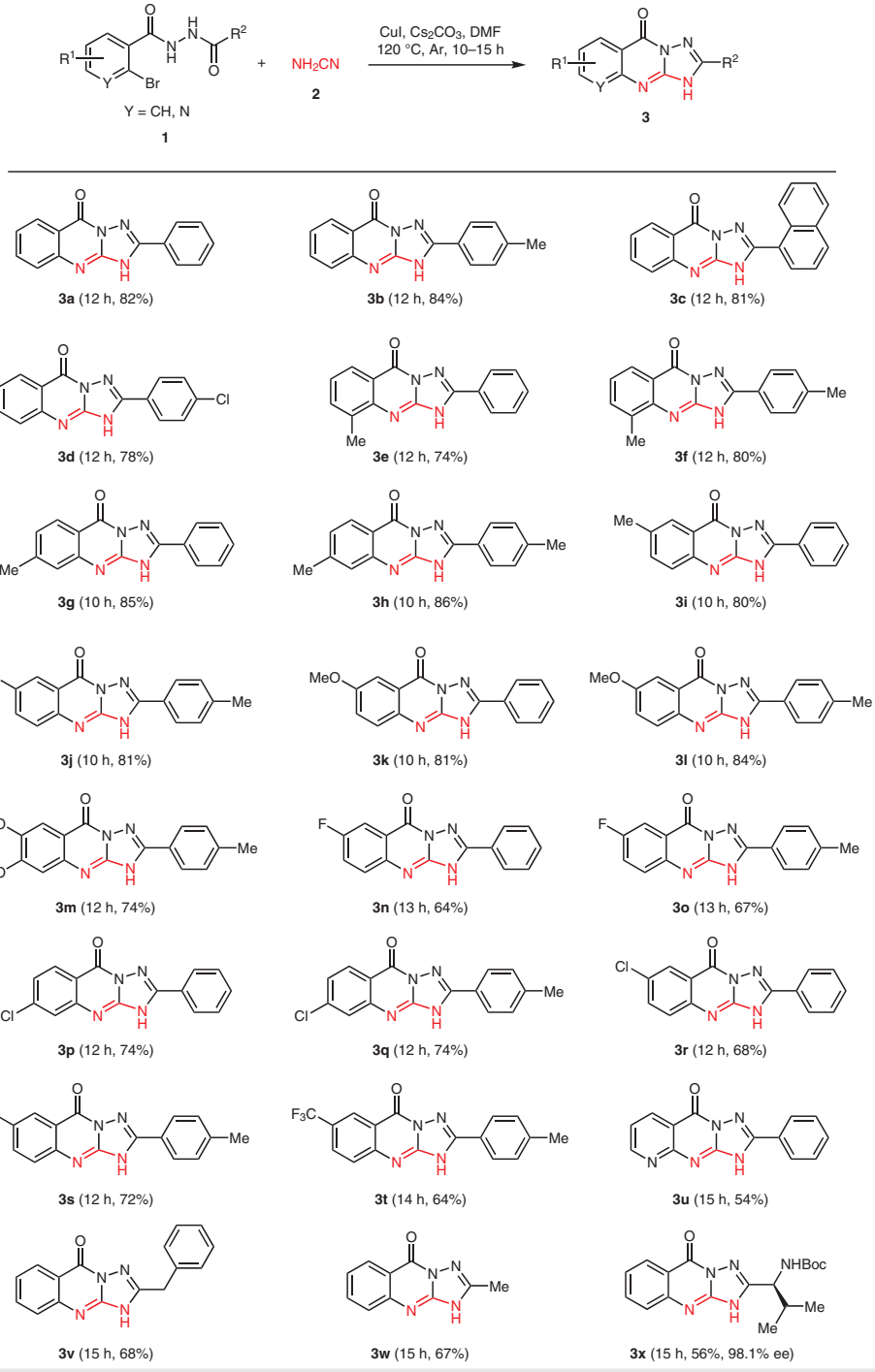
Table 1 Optimization of Conditions for Copper-Catalyzed Domino Reaction of Acetophenone 2-Bromo-*N*′-(4-methylbenzoyl)benzohydrazide (**1b**) with Cyanamide (**2**) Leading to 2-(*p*-Tolyl)-[1,2,4]triazolo[5,1-*b*]quinazolin-9(3*H*)-one (**3b**)[a]



Entry	Cat.	Base	Solvent	Yield (%)[b]
1	CuI	Cs_2CO_3	DMF	84
2	CuBr	Cs_2CO_3	DMF	80
3	CuCl	Cs_2CO_3	DMF	78
4	Cu_2O	Cs_2CO_3	DMF	54
5	$Cu(OAc)_2$	Cs_2CO_3	DMF	64
6	$CuCl_2$	Cs_2CO_3	DMF	56
7	–	Cs_2CO_3	DMF	0
8	CuI	K_2CO_3	DMF	81
9	CuI	K_3PO_4	DMF	80
10	CuI	Cs_2CO_3	DMSO	83
11	CuI	Cs_2CO_3	DMA	84
12	CuI	Cs_2CO_3	dioxane	42
13[c]	CuI	Cs_2CO_3	DMF	84
14[d]	CuI	Cs_2CO_3	DMF	25

[a] Reaction conditions: argon atmosphere, 2-bromo-*N*′-(4-methylbenzoyl)benzohydrazide (**1b**; 0.3 mmol), cyanamide (**2**; 0.45 mmol), catalyst (0.03 mmol), base (0.3 mmol), solvent (3.0 mL), temperature (120 °C), time (12 h) in a sealed Schlenk tube. DMA = *N*,*N*-Dimethylacetamide.
[b] Isolated yield.
[c] Reaction temperature was 130 °C.
[d] Reaction temperature was 100 °C.

b]quinazolin-9(3*H*)-ones via a tandem Aza-Wittig/heterocumulene-mediated annulation.[11] Unfortunately, long procedures were required which is unfavorable for the construction of diverse target molecules. Therefore, it is of importance to develop a convenient and efficient approach to this kind of compounds. Recently, copper-catalyzed cross-couplings have received significant attention,[12] and various N-heterocycles have been prepared via the coupling reac-



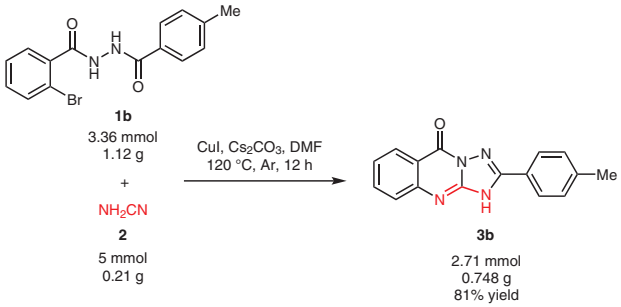
Scheme 1 Copper-catalyzed cascade synthesis of 1,2,4-triazolo[5,1-*b*]quinazolin-9(3*H*)-ones **3**. *Reaction conditions:* argon atmosphere, substituted *N*′-acetyl-2-bromobenzohydrazide **1** (0.3 mmol), cyanamide (**2**; 0.45 mmol), CuI (0.03 mmol), Cs_2CO_3 (0.3 mmol), DMF (3.0 mL), 120 °C, 10–15 h in a sealed Schlenk tube. Isolated yield.

tions by us[13] and other research groups.[14] Herein, we report a novel and efficient copper-catalyzed domino approach to 1,2,4-triazolo[5,1-*b*]quinazolin-9(3*H*)-ones.

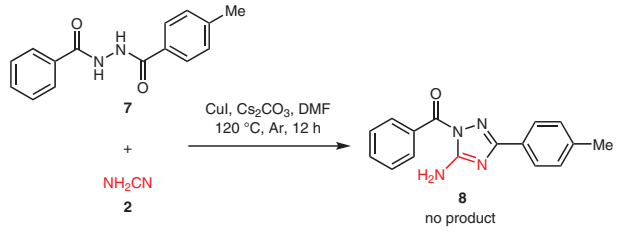
At first, the copper-catalyzed domino reaction of acetophenone 2-bromo-*N*′-(4-methylbenzoyl)benzohydrazide (**1b**) with cyanamide (**2**) leading to 2-(*p*-tolyl)-[1,2,4]triazolo[5,1-*b*]quinazolin-9(3*H*)-one (**3b**) was selected as the model reaction to optimize conditions including catalysts, base, solvents, temperature and time. As shown in Table 1, six catalysts were screened using Cs_2CO_3 as the base and DMF as the solvent under argon atmosphere at 120 °C for 12 hours (Table 1, entries 1–6), and CuI provided the highest yield (Table 1, entry 1). No target product was observed in the absence of copper catalyst (Table 1, entry 7). K_2CO_3 and K_3PO_4 were less efficient bases than Cs_2CO_3 (Table 1, entries 8 and 9). The effect of solvent was investigated (compare entries 1 and 10–12 in Table 1), and DMF was an optimal choice. The reaction temperature was surveyed (compare entries 1, 13 and 14 in Table 1), and a low yield was observed for N-arylation of cyanamide (**2**) when the reaction was performed at 100 °C, so 120 °C was a suitable temperature. Therefore, the optimal conditions for the synthesis of 1,2,4-triazolo[5,1-*b*]quinazolin-9(3*H*)-ones are as follows: 10 mol% CuI as the catalyst, Cs_2CO_3 as the base, and DMF as the solvent under argon atmosphere.

After optimizing the reaction conditions, we investigated the substrate scope for the domino reactions of substituted *N*′-acetyl-2-bromobenzohydrazides **1** with cyanamide (**2**) leading to 1,2,4-triazolo[5,1-*b*]quinazolin-9(3*H*)-ones **3** (Scheme 1).[15] We first surveyed the reactivity of substrates **1** with variation of substituents R^1 when R^2 was an aromatic group, and the substrates containing electron-donating R^1 groups on the aromatic rings provided higher yields than those containing electron-withdrawing R^1 groups (see **3a**–**t**). The substrates containing aliphatic substituents R^2 were also effective (see **3v**–**x**). In particular, product **3x** contains an amino acid residue, and its further modification can afford diverse compounds after removal of the Boc-protecting group. To confirm whether the present method led to ee erosion of **3x**, racemic *rac*-**3′x** was synthesized under the standard conditions. Subsequently, HPLC analysis of *rac*-**3′x** and **3x** was performed with an OD-H chiral column using *n*-hexane/isopropanol (90:10) as the mobile phase (column pressure = 40 bar, flow rate = 1 mL/min), and the results showed that the ee value of **3x** was 98% (see Supporting Information for the details). The copper-catalyzed domino reactions exhibited tolerance of some functional groups including ethers (see **3k**–**m**), C–F bonds (see **3n** and **3o**), C–Cl bonds (see **3p**–**s**), trifluoromethyl (see **3t**), amide (see **3x**), and N-heterocycle (see **3u**).

As shown in Scheme 2, we attempted to scale up the synthesis of 2-(*p*-tolyl)-[1,2,4]triazolo[5,1-*b*]quinazolin-9(3*H*)-one (**3b**) via copper-catalyzed domino reaction of acetophenone 2-bromo-*N*′-(4-methylbenzoyl)benzohydrazide (**1b**; 3.36 mmol, 1.12 g) with cyanamide (**2**; 5.0 mmol, 0.21 g) under the standard conditions, and the target product **3b** was obtained in 81% yield. The result showed that the method was very useful for the synthesis of [1,2,4]-triazoloquinazolinones.



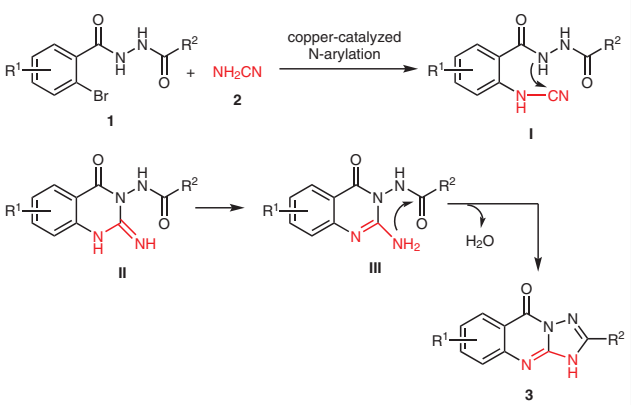
Scheme 2 Scale-up of the copper-catalyzed synthesis of 2-(*p*-tolyl)-[1,2,4]triazolo[5,1-*b*]quinazolin-9(3*H*)-one (**3b**) under the standard conditions



Scheme 3 Copper-catalyzed treatment of *N*′-benzoyl-4-methylbenzohydrazide (**7**) with cyanamide (**2**)

To explore the mechanism of the copper-catalyzed domino reaction, we investigated the treatment of *N*′-benzoyl-4-methylbenzohydrazide (**7**) with cyanamide (**2**) under the standard conditions (Scheme 3). No product **8** was observed, which showed that the copper-catalyzed N-arylation of cyanamide (**2**) with aryl bromide was the initial step for the synthesis of 1,2,4-triazolo[5,1-*b*]quinazolin-9(3*H*)-ones **3**. Therefore, a possible mechanism for the copper-catalyzed domino reactions is proposed in Scheme 4 according to the present results and our previous reports.[13j,k] First, copper-catalyzed N-arylation of cyanamide (**2**) with substituted *N*′-acetyl-2-bromobenzohydrazide **1** affords **I**, and intramolecular nucleophilic addition of NH to CN in **I** gives **II**. Isomerization of **II** leads to **III**, and intramolecular nucleophilic attack of amino to carbonyl in **III** provides the target product **3** leaving water.

In summary, we have developed a novel, efficient, and practical copper-catalyzed domino reaction of substituted *N*′-acetyl-2-bromobenzohydrazides with cyanamide leading to 1,2,4-triazolo[5,1-*b*]quinazolin-9(3*H*)-ones, and the corresponding products were obtained in good to excellent yields. The present method has some advantages including inexpensive CuI as the catalyst, use of readily available



Scheme 4 A possible mechanism for the copper-catalyzed domino reaction of substituted *N*′-acetyl-2-bromobenzohydrazides **1** with cyanamide (**2**)

starting materials, adoption of economical domino reactions and tolerance of a broad range of functional groups. Therefore, this domino strategy can be used in the synthesis of other N-heterocycles.

Funding Information

Financial support from the National Natural Science Foundation of China (Grant No. 21772108) is gratefully acknowledged.

Acknowledgments

We thank Dr. Haifang Li in Department of Chemistry at Tsinghua University for her great help in mass spectrometric analysis.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591565.

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(15) **General Procedures for the Preparation of Compounds 3a–w**: A Schlenk tube was charged with a mixture of CuI (0.03 mmol, 5.7 mg), Cs_2CO_3 (0.3 mmol, 98 mg), substituted *N*′-acetyl-2-bromobenzohydrazide **1** (0.3 mmol), cyanamide (**2**; 0.45 mmol, 19 mg) and anhyd DMF (3.0 mL). After being evacuated and recharged with Ar for three times, the tube was sealed and the mixture was allowed to stir at 120 °C for 10–15 h. After completion of the reaction, the mixture was cooled to r.t., and H_2O (20 mL) was added to the mixture. The solution was extracted with CH_2Cl_2–MeOH (10:1; 3 × 10 mL), and the combined organic layers were dried over anhyd Na_2SO_4. The solution was concentrated, and the residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH = 30:1 or 20:1) providing the target product (**3a–x**). Three representative examples are shown as follows:

6-Methyl-2-phenyl-[1,2,4]triazolo[5,1-*b*]quinazolin-9(3*H*)-one (**3e**): eluent: CH_2Cl_2–MeOH = 30:1. Isolated yield: 85% (70.4 mg); white solid; mp 352–353 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.16 (d, *J* = 6.5 Hz, 2 H), 8.11 (d, *J* = 8.2 Hz, 1 H), 7.54 (q, *J* = 6.4 Hz, 3 H), 7.27 (s, 1 H), 7.21 (d, *J* = 8.2 Hz, 1 H), 2.47 (s, 3 H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 161.6, 155.4, 151.5, 145.9, 139.5, 130.4, 130.1, 128.9 (2 × CH), 127.4, 126.7 (2 × CH), 124.4, 116.3, 111.3, 21.6. ESI–HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{12}N_4NaO$: 299.0903; found: 299.0906.

7-Chloro-2-phenyl-[1,2,4]triazolo[5,1-b]quinazolin-9(3*H*)-one (**3r**): eluent: CH_2Cl_2–MeOH = 30:1. Isolated yield: 68% (60.4 mg); white solid; mp 281–283 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.14–8.19 (m, 3 H), 7.88 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.51–7.58 (m, 4 H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 161.6, 155.0, 151.3, 139.1, 134.5, 131.1, 129.9, 128.3 (2 × CH), 127.9, 127.1, 126.5 (2 × CH), 122.4, 116.6. ESI–HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{10}ClN_4O$: 297.0538; found: 297.0540.

2-Methyl-[1,2,4]triazolo[5,1-*b*]quinazolin-9(3*H*)-one (**3w**): eluent: CH_2Cl_2–MeOH = 30:1. Reaction time: 15 h. Isolated yield: 67% (40.3 mg); white solid; mp 312–314 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.16 (d, *J* = 7.7 Hz, 1 H), 7.78 (t, *J* = 7.4 Hz, 1 H), 7.50 (d, *J* = 7.9 Hz, 1 H), 7.33 (t, *J* = 7.5 Hz, 1 H), 2.36 (s, 3 H). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 161.9, 155.2, 151.0, 139.7, 134.8, 127.3, 122.6, 117.2, 113.3, 14.4. ESI–HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{10}H_9N_4O$: 201.0771; found: 201.0770.