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Water-Mediated Selective Synthesis of Pyrazolo[1,5-*a*]quinazolin-5(4*H*)-ones and [1,2,4]Triazolo[1,5-*a*]quinazolin-5(4*H*)-one via Copper-Catalyzed Cascade Reactions

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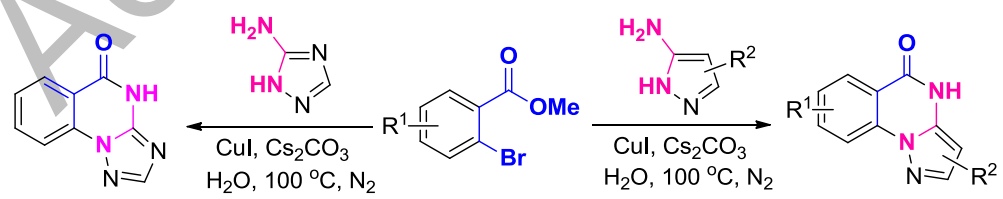
Abstract

A convenient and sustainable synthesis of pyrazolo[1,5-*a*]quinazolin-5(4*H*)-ones and [1,2,4]triazolo[1,5-*a*]quinazolin-5(4*H*)-one through copper-catalyzed cascade reactions of 2-bromobenzoates with 1*H*-pyrazol-5-amines or 1*H*-1,2,4-triazol-5-amine under ligand-free conditions in water is presented. It is notable that aqueous medium turned out to be crucial for the chemoselective formation of the title compounds. Compared with literature protocols, this new method showed advantages such as simple and sustainable procedure, commercially available starting materials, and convenient reuse of the reaction medium together with the copper catalyst.

GRAPHICAL ABSTRACT



KEYWORDS: Pyrazolo[1,5-*a*]quinazolinone; [1,2,4]triazolo[1,5-*a*]quinazolinone; Copper catalysis; Cascade reaction

INTRODUCTION

Pyrazoloquinazolinone is a privileged scaffold frequently found in compounds possessing remarkable pharmacological activities including anti-allergic, anti-parasitic and anti-inflammatory.[1-3] In addition, some pyrazoloquinazolinone derivatives have been developed as potential cytokines TNF-α and IL-1β modulator,[4] polymerase-1 inhibitor, and topoisomerase I inhibitor.[5] Owing to their importance, a number of methods have been developed for the preparation of pyrazoloquinazolinones. For example, Taliani reported that this class of compounds could be obtained *via* the reaction of 5*H*-pyrazolo [1,5-*a*][3,1]benzoxazin-5-one with amines.[5] In another approach, pyrazoloquinazolinones were synthesized through condensing α-cyanoketones with 2-hydrazinobenzoic acids.[2,6] More recently, Bao developed an elegant strategy in which pyrazoloquinazolinone and its aza-analogues were obtained *via* the reaction of 2-halobenzamides with different *N*-heterocycles through a Cu(I)-catalyzed C-N coupling/C-H activation/C-N formation cascade process.[7] While these literature protocols are generally efficient and reliable, some of them still suffer from delicate substrates, tedious procedures and harsh reaction conditions. Therefore, new synthetic methods starting from readily available substrates and realized in a more environmentally sustainable manner are highly desirable.

In recent years, a rapidly growing interest has been devoted to water as an alternative

solvent for organic reactions.[8] It has been well demonstrated that a wide range of reactions can be realized efficiently in water. In addition, industry is increasingly adopting water as a solvent. The strong motive behind this trend is mostly attributed to the urgent desire for "greener" and "cleaner" chemistry. In addition to being safe, cheap, and environmentally sustainable, water as solvent also offers better selectivity, faster reaction rates, and higher yields in numerous cases.

Compared with noble metal catalysts, copper compounds are cheaper and easier to handle. In recent years, copper-catalyzed coupling between aryl halides and nitrogen nucleophiles have been widely utilized in the preparation of *N*-heterocycles.[9, 10] In this regard, we have disclosed a straightforward synthetic pathway toward pyrazolo[1,5-*a*]quinazolines *via* copper-catalyzed cascade reactions of 2-bromobenzaldehydes with aminopyrazoles.[11] Following this success, we presumed that under similar conditions, 2-bromobenzoate would react with aminopyrazole to give pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one *via* an amide formation and C-N coupling cascade process. Experimental studies showed that the reaction pattern of 2-bromobenzoate was, however, more complicated than that of 2-bromobenzaldehyde and it was largely dependent on the nature of the reaction medium. Among various reaction medium studied, water was found to be the most suitable for the formation of pyrazolo[1,5-*a*]quinazolin-5(4*H*)-ones from the reaction of 2-bromobenzoates with aminopyrazoles.

RESULTS AND DISCUSSION

Initially, methyl 2-bromobenzoate (**1a**) was treated with 1*H*-pyrazol-5-amine (**2a**) in the presence of K_2CO_3, CuI, and en in DMF at 110 °C for 5 h.[11] From this reaction, the desired pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one (**3a**) was obtained but in low yield (8%, Table 1, entry 1). Along with **3a**, the unexpected 5-methoxypyrazolo[1,5-*a*]quinazoline (**4**), a by-product, was obtained in a yield of 10% (entry 1). In order to improve the reaction in terms of efficiency and chemo-selectivity, L-proline or 1,10-phen was tried as an additive. However, they were found to be no more effective than en (entries 2 and 3). When Cs_2CO_3 was used to replace K_2CO_3 as the basic promoter, the yields of **3a** and **4** increased obviously. However, addition of en, L-proline, or 1,10-phen did not give better yields (entries 4-7). Next, switching the solvent from DMF to DMSO, THF, or *i*-PrOH did not give satisfying results (entries 8-10). Gratifyingly, when a mixed solvent of DMF and water was used, the yield of **3a** increased along with the growing ratio of water (entries 11-14). When only water was used as the reaction medium, **3a** was obtained in a yield of 61% while **4** was formed only in a trace amount (entry 15). Under a nitrogen atmosphere, the yield of **3a** could be further improved to 70% (entry 16). Further attempt to improve the reaction by using en, L-proline, 1,10-phen, DMEDA, or TMEDA as an additive (entries 17-21), and CuBr or $Cu(OAc)_2$ as a catalyst turned out to be not productive (entries 22-23). In summary of the optimization study, treating **1a** and **2a** with 0.2 equiv of CuI, 2 equiv of Cs_2CO_3 in water under N_2 at 100 ºC for 6 h afforded **3a** in a yield of 70%.

With the optimized conditions in hand, the scope and generality of this novel synthesis of pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one was studied. As a first aspect, 2-bromobenzoates (**1**) with different substituents on the phenyl ring were reacted with 5-aminopyrazole (**2a**). The results listed in Table 2 showed that the R^1 unit of **1** can be hydrogen (entry 1), chloro (entry 2), the electron-donating methoxy (entry 3), or the electron-withdrawing nitro group (entries 4-5), without showing obvious electronic or steric effects. Furthermore, diversely substituted aminopyrazoles (**2**) were tested for this reaction. The results listed in Table 3 showed that methyl, cyclopropyl, phenyl, or 2-thienyl substituted aminopyrazoles reacted with **1a** smoothly to afford **3f-3i** with reasonable efficiency (Table 3, entries 1-4). To our delight, 4-cyanoaminopyrazole, an aminopyrazole with a strong electron-withdrawing substituent on the pyrazole ring, could also take part in this reaction albeit the yield was lower (entry 5). In following study, various 2-bromobenzoates **1** bearing different functional groups on the phenyl ring were allowed to react with different aminopyrazoles **2**. It turned out that all the substrates studied were compatible for this cascade reaction to give **3k-3t** in moderate yields (entries 6-15). Having established a simple and general method for the preparation of pyrazolo[1,5-*a*]quinazolines, we were then interested in using this strategy to prepare another kind of fused *N*-heterocycle, [1,2,4]triazolo[1,5-*a*]quinazolin-5(4*H*)-one, which has been proved to be biologically significant.[12] Thus, methyl 2-bromobenzoate (**1a**) was treated with 1*H*-1,2,4-triazol-5-amine (**5**) under the optimum reaction conditions for the preparation of **3a** (Table 1, entry 16). We were pleased to found that the expected [1,2,4]triazolo[1,5-*a*]quinazolin-5(4*H*)-one (**6**) could be successfully obtained from this reaction in a yield of 51% (Scheme 1).

Finally, it is notable that the reaction medium together with the catalyst used for the preparation of pyrazoloquinazolinone could be conveniently recovered and efficiently reused. Thus, upon completion of the reaction of **1a** and **2a** under the catalysis of CuI in water, the resulting mixture was extracted with ethyl acetate to collect product **3a** and remove possible side-products. The remaining aqueous phase containing the copper catalyst was directly reused. It turned out that the reaction of **1a** and **2a** using this recycled catalytic system afforded **3a** in a yield of 63%.

Based on the above results, the mechanism for the formation of **3a** is proposed in Scheme 2. The initial nucleophilic addition of **2a** onto **1a** gives intermediate **A**. Elimination of H_2O from **A** would give intermediate **B**, which then undergoes an intramolecular C-N coupling under the catalysis of CuI to afford **4** (pathway **I**). Alternatively, elimination of MeOH from **A** would give rise to intermediate **C**, from which **3a** is formed (pathway **II**). When the reaction is run in DMF, the two pathways are offered with similar opportunity and the selectivity is only marginal. When it is run in water, on the other hand, elimination of MeOH is preferred to that of water as it is suppressed by the presence of an excess amount of H_2O.

The plausible mechanism shown in Scheme 2 was supported in part by the following control experiments. When **1a** was treated with **2a** in H_2O at 100 ^oC in the presence of Cs_2CO_3 for 4 h, it afforded 2-bromo-*N*-(1*H*-pyrazol-5-yl)benzamide (**C**) in a yield of 71%. Addition of 0.2 equiv of CuI and stirring of the resulting mixture for 2 h led to the formation of **3a** in a total yield of 65%.

EXPERIMENTAL

All the starting materials were commercially available reagents and used without further purification. Melting points were recorded with a micro melting point apparatus and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts were reported in ppm from tetramethylsilane (TMS) as internal standard in DMSO-d_6 solution. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublets), td (triplet of doublets), br s (broad singlet), etc., and coupling constants were given in Hz. High-resolution mass spectra (HRMS) were obtained *via* ESI mode by using a MicrOTOF mass spectrometer. All reactions were monitored by thin-layer chromatography (TLC) using silica gel plates (silica gel 60 F254 0.25 mm).

Typical Procedure For The Preparation Of Pyrazolo[1,5-*A*]Quinazolin-5(4*H*)-One (3a)

To a solution of Cs_2CO_3 (2 mmol) in H_2O (5 mL) were added methyl 2-bromobenzoate (**1a**, 1 mmol), 1*H*-pyrazol-5-amine (**2a**, 1.2 mmol), and CuI (0.2 mmol). The mixture was stirred at 100 °C under nitrogen until a complete conversion as indicated by TLC. The mixture was then cooled to room temperature and extracted with ethyl acetate. The combined organic phase was dried over anhydrous Na_2SO_4, and concentrated under vacuum. The crude product was purified by column chromatography eluting with petroleum ether/ethyl acetate (3:1) to give **3a**. Products **3b-3t** and **6** were obtained in a similar manner.

Pyrazolo[1,5-*A*]Quinazolin-5(4*H*)-One (3a):

white solid, mp 284-286 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 5.89 (d, J = 2.0 Hz, 1H), 7.46 (t, J = 7.2 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.84-7.88 (m, 1H), 8.06 (d, J = 8.4 Hz, 1H), 8.12 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 12.21(s,1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 88.9, 114.8, 116.5, 125.7, 128.6, 135.50, 137.8, 139.0, 142.6, 158.9. HRMS calcd for $C_{10}H_8N_3O$: 186.0667 $[M+H]^+$, found: 186.0674.

CONCLUSION

In conclusion, we have developed a simple and sustainable synthesis of diversely substituted pyrazoloquinazolinones *via* copper-catalyzed cascade reactions of 2-bromobenzoates with 5-aminopyrazoles. Using similar strategy, [1,2,4]triazolo[1,5-*a*]quinazolin-5(4*H*)-one could be obtained from the reaction of 2-bromobenzoate with 1*H*-1,2,4-triazol-5-amine. Compared with previous methods for the preparation of pyrazoloquinazolinones, the protocol reported herein has the advantages such as commercially available starting materials, simple synthetic procedures, mild reaction conditions, environmentally benign nature and recyclability of the reaction medium and catalyst.

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Team in Science and Technology in University of Henan Province (15IRTSTHN003), and PCSIRT (IRT 1061) for financial support.

SUPPLEMENTAL MATERIAL

Full experimental detail, ^{1}H and ^{13}C NMR spectra, and HRMS for this article can be accessed on the publisher's website

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Yang, Y.; Liu, Y.; Li, Y. *J. Org. Chem*. **2015**, *80*, 1275; (n) Yuan, X.; Xu, X.; Zhou, X.; Yuan, J. Mai, L.; Li, Y. *J. Org. Chem.* **2007**, *72*, 1510.

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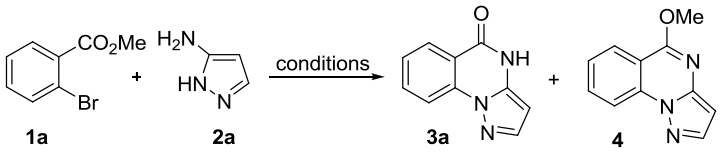
Table 1. Optimization study for the synthesis of **3a** [a]



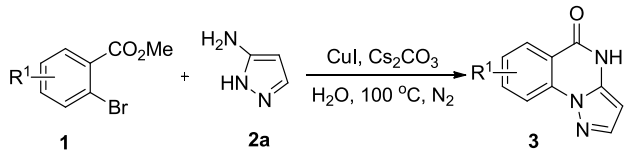
Entry	Catalyst	Solvent	Base	Ligand [b]	T (^oC)	t (h)	Yield(%) [c]	
							3a	**4**
1	CuI	DMF	K_2CO_3	en	110	5	8	10
2	CuI	DMF	K_2CO_3	L-proline	110	5	9	11
3	CuI	DMF	K_2CO_3	1,10-phen	110	5	12	10
4	CuI	DMF	Cs_2CO_3	en	110	5	33	35
5	CuI	DMF	Cs_2CO_3	L-proline	110	5	31	28
6	CuI	DMF	Cs_2CO_3	1,10-phen	110	5	34	36
7	CuI	DMF	Cs_2CO_3	-	110	6	36	32
8	CuI	DMSO	Cs_2CO_3	-	110	6	20	20
9	CuI	THF	Cs_2CO_3	-	reflux	6	trace	trace
10	CuI	i-PrOH	Cs_2CO_3	-	reflu	6	12	11

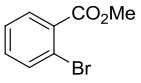
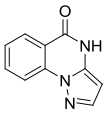
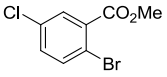
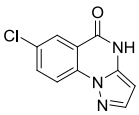
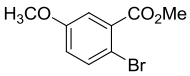
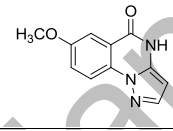
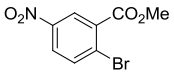
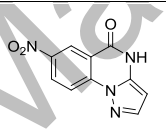
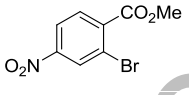
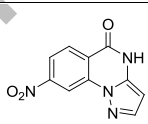
					x			
11	CuI	$V_{(DMF)}$/ $V_{(H2O)}$=2:1	Cs_2CO_3	-	100	6	44	8
12	CuI	$V_{(DMF)}$/ $V_{(H2O)}$=1:1	Cs_2CO_3	-	100	6	48	8
13	CuI	$V_{(DMF)}$/ $V_{(H2O)}$=1:2	Cs_2CO_3	-	100	6	56	trace
14	CuI	$V_{(DMF)}$/ $V_{(H2O)}$=1:3	Cs_2CO_3	-	100	6	58	trace
15	CuI	H_2O	Cs_2CO_3	-	100	6	61	trace
16[d]	CuI	H_2O	Cs_2CO_3	-	100	6	70	trace
17[d]	CuI	H_2O	Cs_2CO_3	en	100	6	71	trace
18[d]	CuI	H_2O	Cs_2CO_3	L-proline	100	6	65	trace
19[d]	CuI	H_2O	Cs_2CO_3	1,10-phen	100	6	64	trace
20[d]	CuI	H_2O	Cs_2CO_3	DMEDA	100	6	62	trace
21[d]	CuI	H_2O	Cs_2CO_3	TMEDA	100	6	58	trace
22[d]	CuBr	H_2O	Cs_2CO_3	-	100	6	55	trace

23[d]	$Cu(OAc)_2$	H_2O	Cs_2CO_3	-	100	6	57	trace

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), base (1 mmol), catalyst (0.1 mmol), solvent (3 mL). [b] Ligand: ethylenediamine (en), L-proline, 1,10-phenanthroline (1,10-phen), *N*, *N*'-dimethylethylenediamine (DMEDA), and *N*, *N*, *N*', *N*'-tetramethylethylene diamine (TMEDA). The amount of ligand is 0.2 equiv. [c] Isolated yield. [d] Under nitrogen atmosphere.

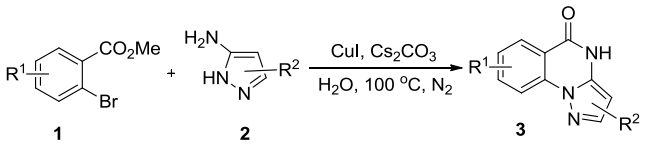
Table 2. Substrate scope for the synthesis of **3** (I) [a]

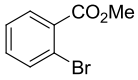
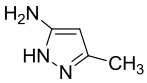
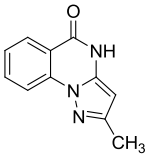
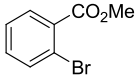
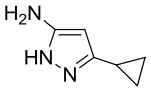
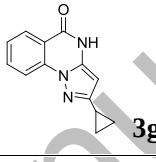
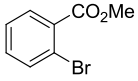
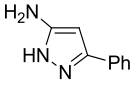
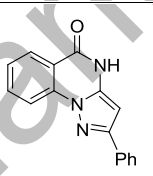
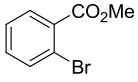
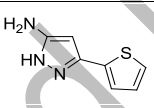
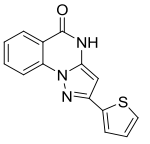
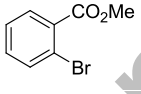
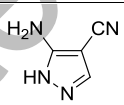
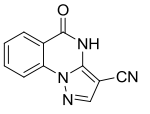
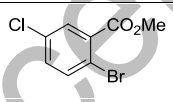
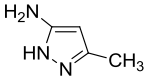
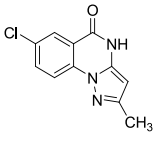
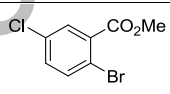
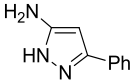
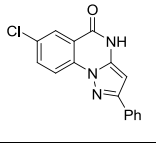
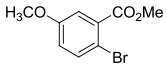
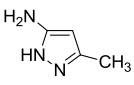
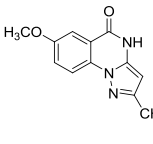


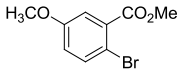
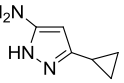
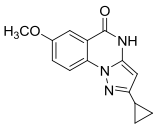
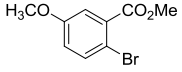
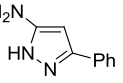
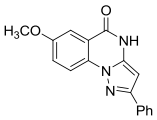
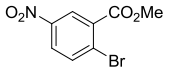
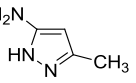
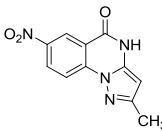
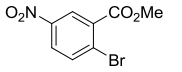
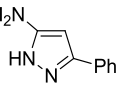
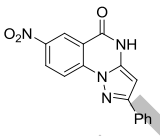
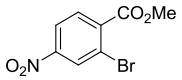
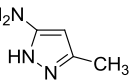
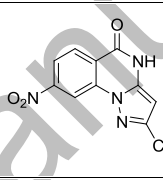
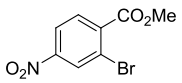
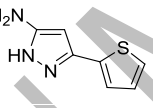
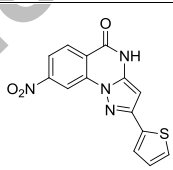
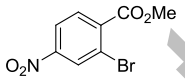
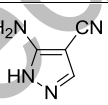
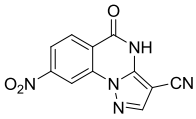
Entry	**1**	**3**	Yield (%)[b]
1		 **3a**	70
2		 **3b**	56
3		 **3c**	62
4		 **3d**	58
5		 **3e**	65

[a] Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), CuI (0.2 mmol), Cs_2CO_3 (2 mmol), H_2O (5 mL), 100 °C, N_2, 6 h. [b] Isolated yield.

Table 3. Substrate scope for the synthesis of **3** (II) [a]

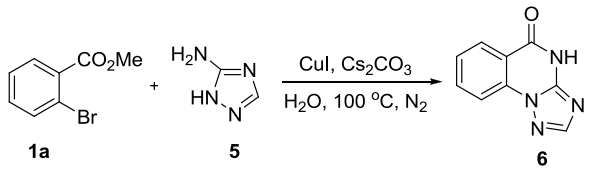


Entry	1	2	3	Yield (%)[b]
1			 **3f**	75
2			 **3g**	62
3			 **3h**	61
4			 **3i**	54
5			 **3j**	45
6			 **3k**	62
7			 **3l**	57
8			 **3m**	64

9			 **3n**	51
10			 **3o**	52
11			 **3p**	64
12			 **3q**	63
13			 **3r**	70
14			 **3s**	52
15			 **3t**	42

[a] Reaction conditions: 1 (1 mmol), 2 (1.2 mmol), CuI (0.2 mmol), Cs_2CO_3 (2 mmol), H_2O (5 mL), 100 ^oC, N_2, 6 h. [b] Isolated yield.

Scheme 1. Synthesis of [1,2,4]triazolo[1,5-*a*]quinazolin-5(4*H*)-one (**6**)



Scheme 2. Plausible mechanism for the formation of **3a**