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Chitosan-Supported CuI-Catalyzed Cascade Reaction of 2-Halobenzoic Acids and Amidines for the Synthesis of Quinazolinones

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Abstract

A chitosan-supported CuI (CS@CuI) catalyst was developed for the synthesis of quinazolinones from 2-halobenzoic acids (including iodine and bromine) and amidines. The reaction proceeds under mild reaction conditions, demonstrating a broad substrate scope (30 examples) and good catalytic efficiency (up to 99% yield).

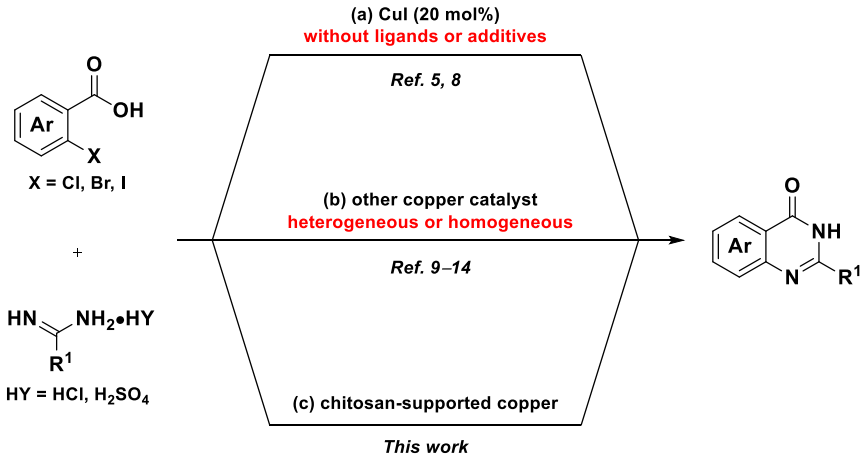
Keywords

chitosan-supported CuI catalyst; cyclization reaction; quinazolinone; mild condition

Introduction

Quinazolinones are key core benzoazo heterocyclics found in many natural products and bioactive molecules. [1−3] Due to their significant biological relevance, numerous synthetic methods have been recently developed to synthesize these useful intermediates. [4−7] Among these methods, the cascade reaction between ortho-halogen (e.g. chlorine, bromine or iodine) substituted benzoic acids and amidines has become a prominent route to synthesize the corresponding quinazolinones. [8−16] In 2009, Fu and co-workers found that copper(I) could effectively promote this cascade reaction for the synthesis of quinazolinones without the need for additional ligands or additives (Scheme 1a). [5,8] Since then, various copper-based catalysts, both homogeneous and heterogeneous, have been explored (Scheme 1b). [9−14] For example, Wang's group developed a magnetically recoverable and reusable Fe_3O_4 nanoparticle-supported copper(I) catalyst with excellent catalytic efficiency for quinazolinone synthesis. [9] In addition, Cai et al. reported that MCM-41-immobilized tridentate nitrogen-supported copper(I) [MCM-41-3N–CuI] served as a highly efficient, reusable heterogeneous catalyst for this cascade reaction, achieving good to excellent yields without any loss of activity even after ten cycles of simple filtration-based recovery. [10] Moreover, copper catalyst has been shown to function effectively in both organic and aqueous media. [11,12] Furthermore, dicopper(I) complexes can also be used as an effective catalyst in Ullmann-type *N*-arylation/cyclization of 2-bromobenzoic acids with amidines, providing the corresponding quinazolinones in good yields. [13] Despite the high efficiency of above copper catalysts in the synthesis of quinazolinones, and the wide application of chitosan-supported copper catalyst in various organic transformations, [17−19] the use of chitosan-supported copper for quinazolinone synthesis has not been reported until now. As part of our ongoing

research interest in chitosan and chitosan-supported copper catalysts in organic transformations, [20−22] we intended to investigate the use of chitosan-supported copper as a catalyst for the synthesis of quinazolinones from 2-halobenzoic acids and amidines under mild reaction conditions (Scheme 1c).



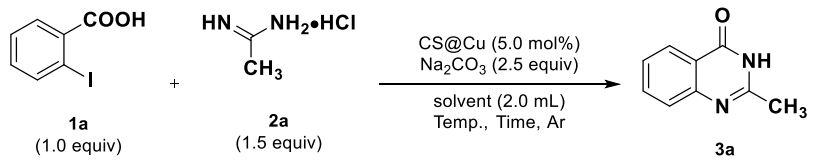
Scheme 1: Copper-catalyzed cascade reaction of 2-halobenzoic acids and amidines for the synthesis of quinazolinones

Results and Discussion

The initial reactions commenced with 2-iodobenzoic acid **1a** (0.5 mmol, 1.0 equiv) and acetamidine hydrochloride **2a** (0.75 mmol, 1.5 equiv) as model substrates, Na_2CO_3 (1.25 mmol, 2.5 equiv) as a base, and chitosan-supported copper (5.0 mol%) as the catalyst under an argon atmosphere (Table 1). First, various solvents were investigated. When nonprotonated solvents such as THF and toluene were used, the yields were relatively low (entries 1−2, 27−39% yields), indicating poor catalytic activity in these solvents. In contrast, using proton solvents (MeOH, *i*-PrOH and H_2O) led to improved yields (entries 3−5, 51−60% yields). Notably, the reaction was also successful in water, affording the target product in moderate yield (entry 5, 51% yield). Next, to further improve the yield, a mixed solvent of *i*-PrOH and H_2O was examined.

The reaction conducted with a solvent ratio of *i*-PrOH:H_2O = 4:1 gave an 84% yield (entry 6), while a ratio of *i*-PrOH:H_2O = 9:1 resulted in an 89% yield (entry 7). In the optimal solvent (*i*-PrOH: H_2O = 9:1), other chitosan supported copper catalysts, such as CS@CuBr, CS@Cu(OAc)$_2$, CS@Cu(acac)$_2$ and CS@$CuSO_4$ were explored, and the results showed that CS@CuI was the most effective catalyst (entries 7−11, 65−89% yields). To further enhance the reaction, the reaction temperature was increased to 90 °C, and the target product **3a** was obtained in 96% isolated yield (entry 12). Control experiments indicated poor results when no catalyst was used, with the corresponding product obtained only in 31% yield (entry 13). When CuI or chitosan alone was used as a catalyst, the reaction occurred but with less efficiency (entries 14−15, 40−80% yields). In addition, when the reaction time was reduced, the yields decreased accordingly (entries 16−18, 70−94% yields). Finally, when the reaction was carried out under open air, the catalytic activity decreased and only 45% yield of the target product was obtained (entry 19).

Table 1: Optimization of reaction conditions[a]



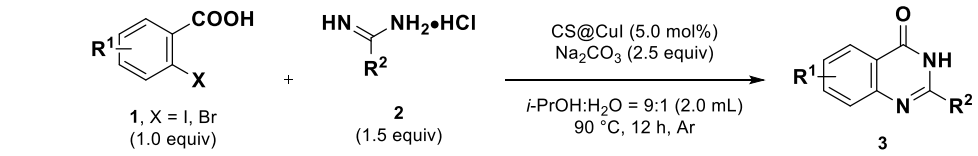
Entry	CS@Cu	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	CS@CuI	THF	80	12	39
2	CS@CuI	Toluene	80	12	27
3	CS@CuI	MeOH	80	12	55
4	CS@CuI	*i*-PrOH	80	12	60
5	CS@CuI	H_2O	80	12	51
6	CS@CuI	*i*-PrOH: H_2O (4:1)	80	12	83
7	CS@CuI	*i*-PrOH: H_2O (9:1)	80	12	89
8	CS@CuBr	*i*-PrOH: H_2O (9:1)	80	12	87
9	CS@Cu(OAc)$_2$	*i*-PrOH: H_2O (9:1)	80	12	65

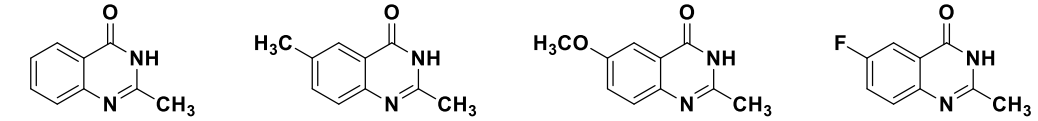
10	CS@Cu(acac)$_2$	*i*-PrOH: H_2O (9:1)	80	12	65
11	CS@$CuSO_4$	*i*-PrOH: H_2O (9:1)	80	12	67
12	**CS@CuI**	***i*-PrOH: H_2O (9:1)**	**90**	**12**	**99 (96)[c]**
13	-	*i*-PrOH: H_2O (9:1)	90	12	31
14	CuI	*i*-PrOH: H_2O (9:1)	90	12	80
15	CS	*i*-PrOH: H_2O (9:1)	90	12	40
16	CS@CuI	*i*-PrOH: H_2O (9:1)	90	8	94
17	CS@CuI	*i*-PrOH: H_2O (9:1)	90	5	83
18	CS@CuI	*i*-PrOH: H_2O (9:1)	90	3	70
19[d]	CS@CuI	*i*-PrOH: H_2O (9:1)	90	12	45

[a]Reaction conditions: **1a** (0.5 mmol, 1.0 equiv), acetamidine hydrochloride **2a** (0.75 mmol, 1.5 equiv), CS@Cu (5.0 mol%), Na_2CO_3 (1.25 mmol, 2.5 equiv), solvent (2.0 mL) at argon atmosphere. [b]The yield was determined by ^{1}H NMR analysis with dibromomethane as an internal standard. [c]Isolated yield in parentheses. [d]The reaction was performed under open air.

With the optimized conditions in hand, we explored the substrate scope of the CS@CuI catalyzed cascade reactions of 2-halobenzoic acids (including 2-iodobenzoic acid and 2-bromobenzoic acid) with amidines (Scheme 2). Initially, when the amidine substituent (R^2) is a methyl group, we investigated the reactions with various substituted 2-halobenzoic acids. The reactivity of 2-iodobenzoic acid derivatives (**3a**−**3d**, 90−96% yields) was higher than that of 2-bromobenzoic acid derivatives (**3a**−**3d**, 57−73% yields), the electronic properties of the substituents on the benzene ring had little effect on the reactivity. When the amidine substituent (R^2) was changed to a cyclopropyl group, the yields of all reactions decrease, especially when substituents were present on the benzene ring (**3e**−**3h**, 55−94% yields for 2-iodobenzoic acid, 43−76% yields for 2-bromobenzoic acid). We then investigated the reactions of different 2-halobenzoic acid derivatives with amidines where R^2 was a *tert*-

butyl group. The results showed that 2-bromobenzoic acid derivatives (**3j**−**3k**, 55−65% yields) displayed lower activity compared to 2-iodobenzoic acid derivatives (**3i**−**3l**, 73−90% yields), with a decrease in reaction activity observed when substituents were presented on the benzene ring. Finally, we examined reactions with 2-halobenzoic acid derivatives where the R^2 substituent was a phenyl group. In this case, the reactivity of 2-iodobenzoic acid derivatives (**3m**−**3p**, 61−99% yields) was again superior to that of 2-bromobenzoic acid derivatives (**3m**−**3p**, 43−68% yields). The reactivity of 2-halobenzoic acid without substituents was obviously better than that of substituted derivatives. Overall, these results demonstrate that the reaction has a broad substrate scope, with 2-iodobenzoic acid derivatives showing higher reactivity than 2-bromobenzoic acid derivatives.



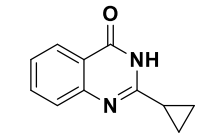


3a
X = I, 96%;
X = Br, 73%[b]

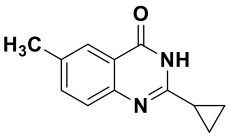
3b
X = I, 93%;
X = Br, 64%[b]

3c
X = I, 90%;
X = Br, 57%[b]

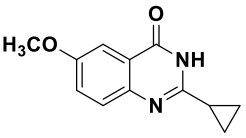
3d
X = I, 94%;
X = Br, 62%[b]



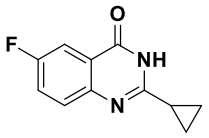
3e
X = I, 94%;
X = Br, 76%[b]



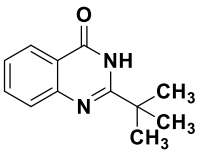
3f
X = I, 55%;
X = Br, 43%[b]



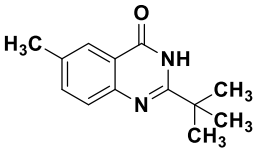
3g
X = I, 78%;
X = Br, 59%[b]



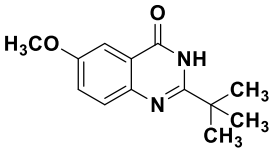
3h
X = I, 78%;
X = Br, 62%[b]



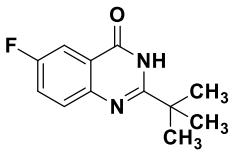
3i
X = I, 90%



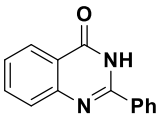
3j
X = I, 79%;
X = Br, 55%[b]



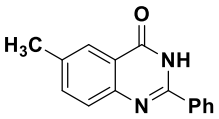
3k
X = I, 80%;
X = Br, 65%[b]



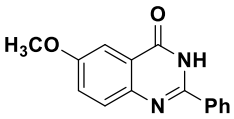
3l
X = I, 73%



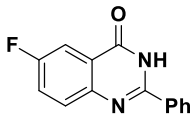
3m
X = I, 99%;
X = Br, 68%[b]



3n
X = I, 70%;
X = Br, 57%[b]



3o
X = I, 72%;
X = Br, 61%[b]



3p
X = I, 61%;
X = Br, 43%[b]

Scheme 2: Substrate scope. [a]Reaction conditions: **1** (0.5 mmol, 1.0 equiv), amidines hydrochloride **2** (0.75 mmol, 1.5 equiv), CS@CuI (10.0 mg, ICP: 14.6%, 5.0 mol%), Na_2CO_3 (1.25 mmol, 2.5 equiv), *i*-PrOH: H_2O = 9:1 (2.0 mL), 90 ^oC, 12 h, argon atmosphere; [b]**1** (0.2 mmol), amidines hydrochloride **2** (0.3 mmol, 1.5 equiv), CS@CuI (5.0 mol%), Na_2CO_3 (1.25 mmol, 2.5 equiv), *i*-PrOH: H_2O = 9:1 (2.0 mL), 90 ^oC, 12 h, argon atmosphere.

Conclusion

In summary, we have developed a CS@CuI-catalyzed cascade reaction of 2-halobenzoic acids (including iodine and bromine derivatives) and amidines for the synthesis of quinazolinones. This approach features mild reaction conditions, broad substrate scope (30 examples), and high efficiency (up to 99% yield). In a word, this work presents a novel and efficient protocol for the construction of quinazolinones and offers significant research value.

Supporting Information

Supporting Information File 1:

Full experimental details, characterization data and copies of NMR spectra of all products.

Acknowledgements

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