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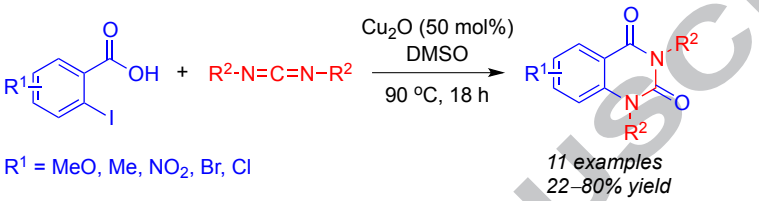

R^1 = MeO, Me, NO_2, Br, Cl

11 examples
22–80% yield

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Copper-catalyzed domino reaction of carbodiimides and benzoic acid derivatives for the synthesis of quinazolinediones

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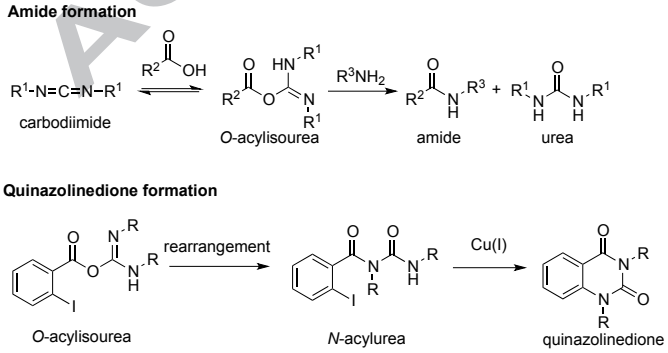
ABSTRACT

Quinazolinediones were obtained from 2-iodobenzoic acids and carbodiimide derivatives under mild reaction conditions *via* a copper-catalyzed domino reaction. The absence of an external base was essential to avoid the generation of amide by-products. Both alkyl- and aryl-substituted carbodiimides gave the corresponding quinazolinediones. However, the use of aryl-substituted carbodiimides resulted in low yields due to an undesired elimination process.

Introduction

Copper-catalyzed domino reactions are a useful method to synthesize organic molecules.[1] In addition, the domino concept allows access to complex molecules from simple starting materials. As part of our interest in the synthesis of *N*-containing heterocycles, we have focused on the search for simple and interesting organic molecules which are potentially suitable for domino processes. Interestingly, carbodiimides could be used to obtain heterocycles *via* domino processes due to their properties, including the electrophilicity of the middle carbon and the presence of a nitrogen donor for C-N bond formation.



Scheme 1. Amide and quinazolinedione formation from carbodiimides.

Carbodiimides have been widely used for amide bond formation. Nakajima and Ikada extensively studied the reaction mechanism for the formation of amides from carbodiimides and carboxylic acids.[2] A key intermediate in this reaction is an *O*-acylisourea adduct; the amide products are formed *via* nucleophilic substitution of the *O*-acylisoureas with amines, and urea is generated as a by-product. Recently, Zhao and co-workers utilized carbodiimides and ethyl-2-aminobenzoates to synthesize quinazolinones.[3] Likewise, Xi and co-workers also used the reaction of carbodiimides with 2-haloanilines to synthesize 2-aminobenzimidazoles.[4] Alternatively, based on the reaction of carbodiimides and benzoic acids, we envisioned that *O*-acylisoureas could be utilized to obtain quinazolinediones *via* a domino process involving rearrangement to form *N*-acylureas, followed by intramolecular copper-catalyzed C-N bond formation (Scheme 1).

Quinazolinediones are important *N*-containing heterocyclic compounds which possess a wide range of biological activities, such as anti-inflammatory, antihypertensive, anticancer, antitumor, and antibacterial properties.[5] Therefore, methodologies for quinazolinedione synthesis have been developed *via* both metal and non-metal catalysis.[6] Herein, we report a straightforward protocol to obtain quinazolinediones *via* a copper-catalyzed domino process under mild reaction conditions.

Results and Discussion

We began our investigation by optimizing the model reaction of commercially available 2-iodobenzoic acid and *N,N'*-dicyclohexylcarbodiimide (DCC) (Table 1). Firstly, we explored a variety of copper salts, such as Cu_2O, CuI, CuBr and $Cu(OAc)_2$ (Entries 1−4). We found that Cu_2O and CuI provided quinazolinedione **3a** in 31% and 21% yield, respectively, whereas CuBr and $Cu(OAc)_2$ were not reactive. Next, various solvents, such as CH_3CN, DMF and toluene were investigated, resulting in 27%, 22% and 0% yield, respectively (Entries 5−7).

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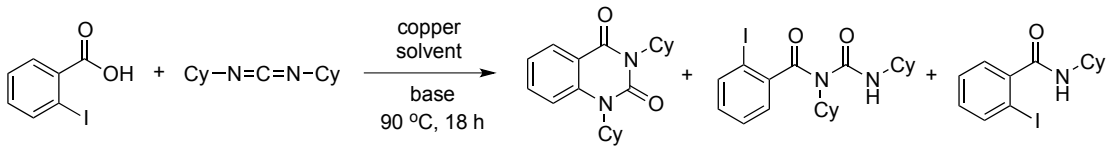
Table 1. Optimization of the reaction conditions.[a]



1a **2a** **3a** **4a** **5a**

Entry	**2a** (equiv.)	Cu (mol%)	Base	Solvent	Yield **3a** (%)[b]
1	1.1	Cu_2O (10)	K_2CO_3	DMSO	31
2	1.1	CuI (10)	K_2CO_3	DMSO	21
3	1.1	CuBr (10)	K_2CO_3	DMSO	trace
4	1.1	$Cu(OAc)_2$ (10)	K_2CO_3	DMSO	trace
5	1.1	Cu_2O (10)	K_2CO_3	CH_3CN	27
6	1.1	Cu_2O (10)	K_2CO_3	DMF	22
7	1.1	Cu_2O (10)	K_2CO_3	toluene	0
8	1.5	Cu_2O (10)	K_2CO_3	DMSO	35
9	2.0	Cu_2O (10)	K_2CO_3	DMSO	38
10	3.0	Cu_2O (10)	K_2CO_3	DMSO	26
11	2.0	Cu_2O (10)	K_3PO_4	DMSO	21
12	2.0	Cu_2O (10)	Cs_2CO_3	DMSO	trace
13	2.0	Cu_2O (10)	NEt_3	DMSO	47
14	2.0	Cu_2O (10)	^{t}BuOK	DMSO	trace
15	2.0	-	-	DMSO	0
16	2.0	Cu_2O (30)	NEt_3	DMSO	64
17	2.0	Cu_2O (50)	NEt_3	DMSO	64
18	2.0	Cu_2O (50)	-	DMSO	75
19	2.0	Cu_2O (10)	-	DMSO	37

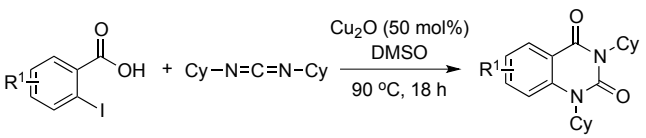
[a]Reagents and conditions: **1a** (0.5 mmol), base (1.5 equiv.).

[b]Isolated yield.

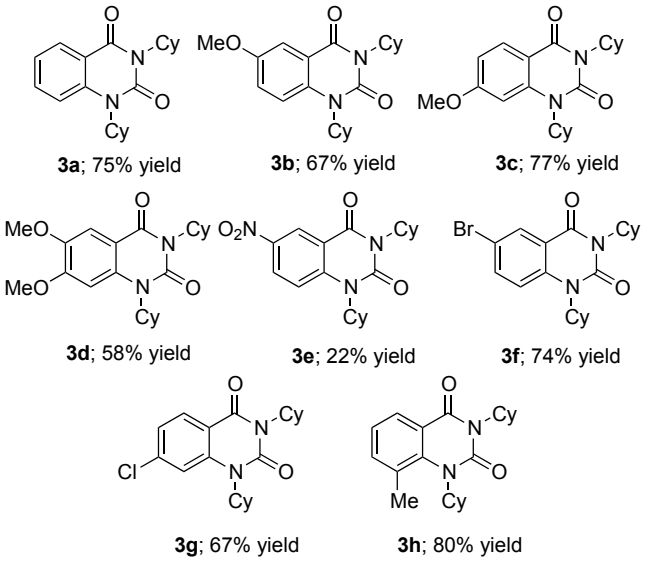
Increasing the amount of carbodiimide slightly increased the product yield (Entries 8−10). However, we found that with three equivalents of carbodiimide the yield was decreased to 26% (Entry 10). Common bases, such as K_3PO_4, Cs_2CO_3, NEt_3 and ^{t}BuOK, were also investigated (Entries 11−14). Unfortunately, none provided good yields, while NEt_3 gave a moderate 47% yield (Entry 13). We found that *N*-acylurea **4a** was exclusively obtained in the absence of a copper catalyst and base (Entry 15). This finding was in agreement with the report from Nakajima and co-workers who showed that benzoic acid reacted with carbodiimides to generate *N*-acylureas without any catalyst.[2] Based on this result, the formation of **4a** was a non-catalyzed reaction pathway. Therefore, in order to improve the product yield we hypothesized that increasing the amount of Cu_2O would enhance the rate of quinazolinedione formation. We then investigated the amount of Cu_2O (Entries 16 and 17). Significantly, the yield was improved to 64% using 30 mol% or 50 mol% of Cu_2O. Additionally, according to a report from Kishikawa and co-workers, **4a** could undergo elimination to give amide **5a** in the presence of base.[7] Crucially, in the absence of an external base the yield of quinazolinedione **3a** was increased to 75% (Entry 18). Non-external base conditions were found to be an important factor to determine the reaction pathway.[8] Unfortunately, lowering the amount of Cu_2O to 10 mol% under non-external base conditions gave low yields of the desired quinazolinedione (Entry 19). Attempts to improve the product yield using cooperating ligands with Cu_2O (10 mol%) resulted in low product yields with high amounts of the amide by-product.

With the optimal reaction conditions in hand (Table 1, entry 18), we further explored the substrate scope using a variety of 2-iodobenzoic acid derivatives (Table 2).

Table 2. Formation of quinazolinediones from 2-iodobenzoic acid derivatives.[a]



1 **2a** **3**



3a; 75% yield **3b**; 67% yield **3c**; 77% yield

3d; 58% yield **3e**; 22% yield **3f**; 74% yield

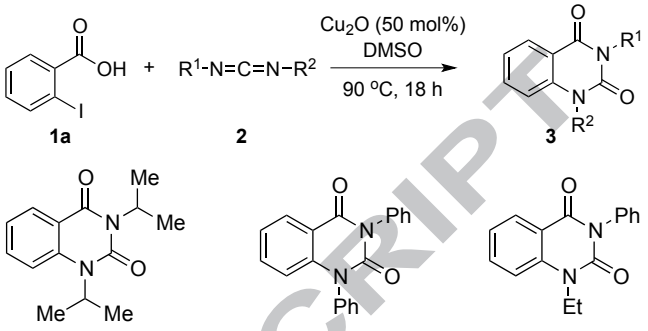
3g; 67% yield **3h**; 80% yield

[a]Reagents and conditions: **1a**−**h** (0.5 mmol), **2a** (1.0 mmol).

The reaction of 2-iodobenzoic acid derivatives bearing electron-donating substituents provided the corresponding quinazolinediones in good yields. Both 2-iodo-5-methoxy- and 2-iodo-4-methoxybenzoic acids gave quinazolinediones **3b** and **3c** in 67% and 77% yield, respectively, while 2-iodobenzoic acid with two methoxy groups provided quinazolinedione **3d** in 58% yield. However, the reaction of 2-iodo-5-nitrobenzoic acid gave quinazolinedione **3e** in only 22% yield. We observed the formation of the corresponding *N*-acylurea as a major by-product. Based on these results, we believe that benzoic acids bearing electron-withdrawing groups preferably undergo the non-catalyzed reaction pathway. Halogen substituents were also applicable to the reaction of 5-bromo-2-iodobenzoic acid which gave quinazolinedione **3f** in 74% yield. Likewise, 4-chloro-2-iodobenzoic acid gave the corresponding quinazolinedione **3g** in 67% yield. Interestingly, the presence of a methyl substituent next to the iodine did not hinder the reaction and provided **3h** in 80% yield.

Next, we examined the scope of the carbodiimides. Three types of carbodiimide were selected: dialkyl (*N*,*N*'-methanediylidenebis(propan-2-amine); **2b**), diaryl (*N*,*N*'-methanediylidenedianiline; **2c**) and an asymmetric carbodiimide (*N*-((ethylimino)methylene)aniline; **2d**) (Table 3). The *N*,*N*'-methanediylidenebis(propan-2-amine) **2b** gave quinazolinedione **3i** in 65% yield. In contrast, **2c** gave low yields of the desired quinazolinedione **3j**. The major product of this reaction was the corresponding amide by-product which was isolated in 58% yield. This result suggested that carbodiimides with diaryl substituents undergo *N*-acylurea formation faster than the copper-catalyzed reaction. Then, elimination of the *N*-acylurea occurs to yield the amide by-product. A similar result was found when the asymmetric carbodiimide was subjected to the reaction, resulting in a low yield of the corresponding 1-ethyl-3-phenylquinazoline-2,4(1*H*,3*H*)-dione **3k**. We did not obtain the other regioisomer, 3-ethyl-1-phenylquinazoline-2,4-(1*H*,3*H*)-dione. Instead, both *N*-ethyl and *N*-phenyl benzamides were obtained, which suggested that the *N*-ethyl-2-iodo-*N*-(phenylcarbamoyl)benzamide intermediate underwent elimination to generate the *N*-ethyl amide by-product faster than that of *N*-(ethylcarbamoyl)-2-iodo-*N*-phenylbenzamide, possibly due to the more acidic proton of the phenylcarbamoyl moiety.

Table 3. Formation of quinazolinediones from a variety of carbodiimides.[a]



1a **2** **3**

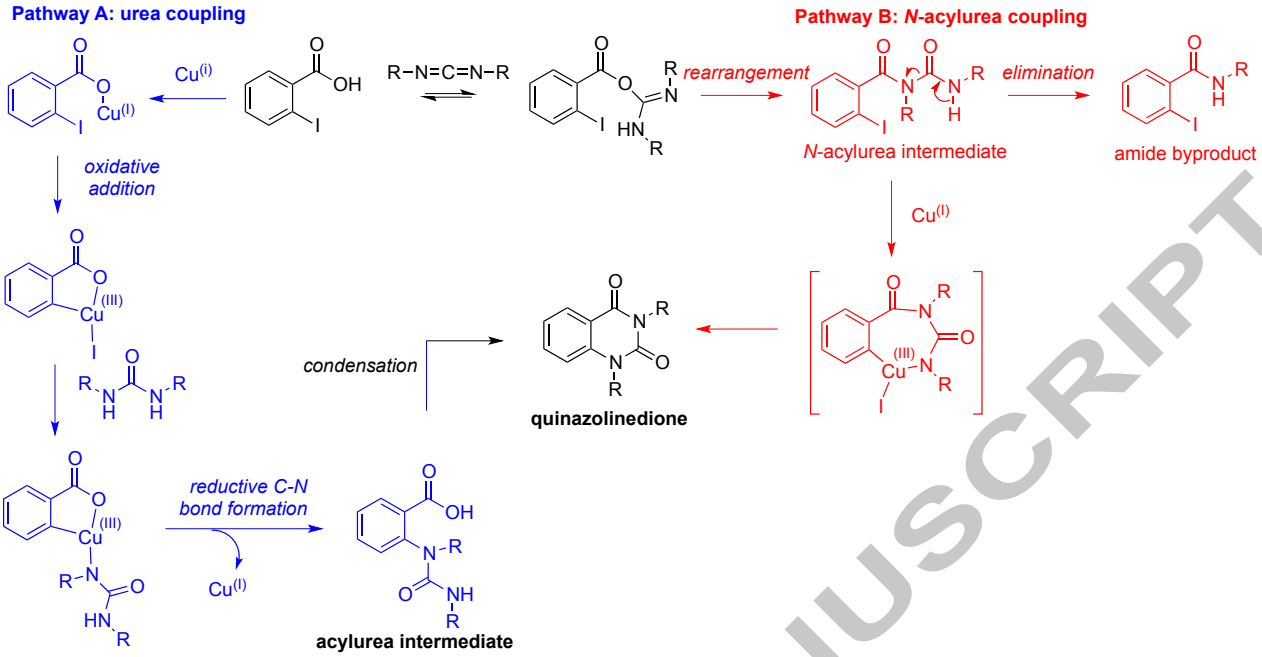
3i; 65% yield **3j**; 30% yield **3k**; 22% yield

[a]Reagents and conditions: **1a** (0.5 mmol), **2** (1.0 mmol).

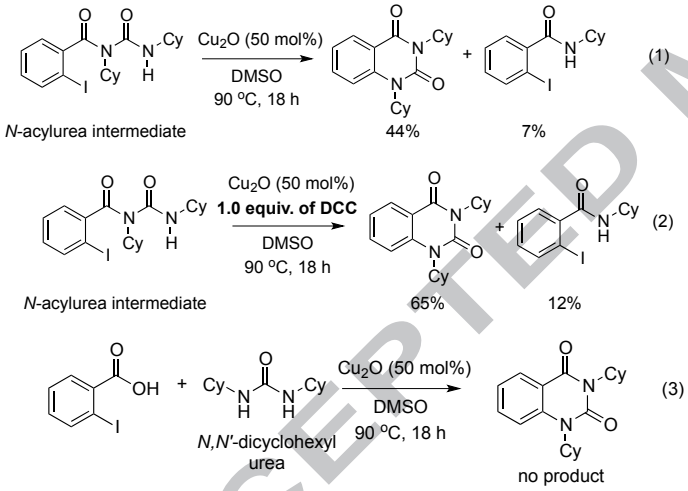
Next, we turned our interest to investigating the reaction mechanism. Since we observed 1,3-dicyclohexylurea formation, we first postulated the mechanism involving a coupling reaction of 2-iodobenzoic acid and the urea generated *in situ* from the reaction of the carbodiimide and moisture in DMSO. Then, an acylurea intermediate undergoes condensation to form the desired product (Scheme 2, pathway A). Secondly, based on our results as well as the reports from Nakajima[2] and Kishikawa[7] related to the role of carbodiimides in amide formation, we postulated that quinazolinediones could be obtained from the copper-catalyzed intramolecular C-N bond formation of an *N*-acylurea intermediate generated from the non-catalyzed reaction of the acid-carbodiimide (Scheme 2, pathway B). The competitive reaction of this pathway was the elimination of an *N*-acylurea intermediate resulting in generation of the amide by-product. Importantly, Perkins and co-workers recently reported the formation of quinazolinediones from *N*-acylureas *via* a copper-catalyzed coupling reaction;[9] these findings supported our second mechanistic postulation.

According to our postulated possible reaction mechanisms, we performed several control experiments (Scheme 3). Due to generation of the amide by-product, we first focused on the pathway involving the *N*-acylurea. The reaction of the *N*-acylurea intermediate under the optimal reaction conditions gave quinazolinedione **3a** and amide **5a** in 44% and 7% yield, respectively, with the *N*-acylurea remaining (Scheme 3, eq. 1). Since the reaction was not complete, and the optimal reaction conditions required 2.0 equivalents of the carbodiimide, another equivalent of *N,N'*-dicyclohexylcarbodiimide was added to the reaction (Scheme 3, eq. 2). The desired product **3a** was obtained in 65% yield and amide **5a** was obtained in 12% yield. This result showed that the excess carbodiimide possibly acted as a base to trigger elimination of the *N*-acylurea intermediate resulting in generation of the amide by-product. Moreover, the yield of **3a** from the second control experiment was similar to the yield using the optimal reaction conditions. Based on these results and the report[9] from Perkins, the quinazolinediones could possibly be synthesized *via* an *N*-acylurea intermediate.

Scheme 2. Possible reaction mechanisms.



Scheme 3. Control experiments.



To examine the possibility of pathway A, *N,N'*-dicyclohexylurea and 2-iodobenzoic acid were subjected to the reaction, however, the desired quinazolinedione was not observed (Scheme 3, eq. 3). Based on this result, we propose that quinazolinediones are not generated from the urea.

Conclusion

The synthesis of quinazolinediones from 2-iodobenzoic acids and carbodiimides *via* a copper-catalyzed domino reaction is reported. The non-catalyzed pathway, leading to *N*-acylureas, crucially impacted the product yields, resulting in the requirement of high copper loading. Non-external base conditions were required in order to minimize the amount of amide by-product resulting from elimination of the *N*-acylurea intermediate. A variety of 2-iodobenzoic acids were applicable, although those with electron-withdrawing substituents provided low yields. Although the exact mechanism could not be determined, based on control experiments we believe that the quinazolinediones are obtained from *N*-acylurea intermediates. Further mechanistic studies are ongoing.

Acknowledgments

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A. Supplementary data

Supplementary data associated with article can be found in the online version, at http://…

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Highlights

- Quinazolinediones were simply synthesized from benzoic acids and carbodiimides.
- A protocol was simple and relatively mild conditions.
- Non-external base was crucial for a desired reaction
- Forming *N*-acylurea was a non-catalyzed reaction leading to both product and byproduct.