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Copper-Catalyzed Cascade Substitution/Cyclization of *N*-Isocyanates: A Synthesis of 1-Aminobenzimidazolones

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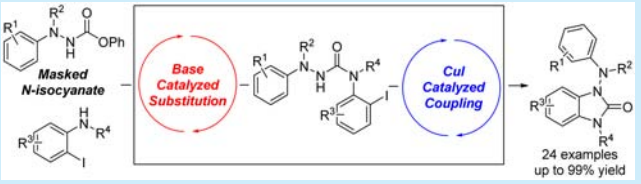
Supporting Information

ABSTRACT: A copper-catalyzed cascade reaction of in situ generated nitrogen-substituted isocyanates (*N*-isocyanates) and 2-iodoanilines has been developed. The cascade relies on the base-catalyzed substitution of masked *N*-isocyanates, followed by Cu(I)-catalyzed coupling to afford a variety of 1-aminobenzimidazolones in moderate to excellent yields. This is the first example of a transition-metal-catalyzed cascade reaction involving *N*-isocyanate intermediates.



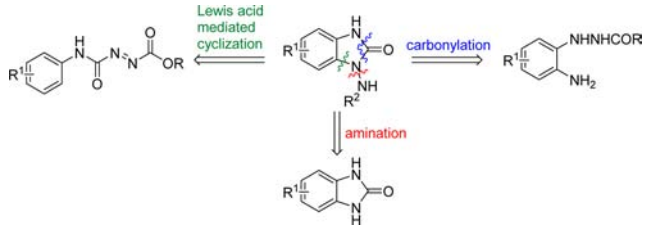
The N−N−C═O motif is widely present in bioactive heterocycles, with over 50 pharmaceuticals and agrochemicals incorporating this structural unit.[1] In particular, the 4-phenylsemicabazide moiety is associated with remarkable biological properties.[2] For example, pyrifluquinazon[3] is a new insecticide for the control of sucking pests. Selurampanel[4] is an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/Kainate receptor antagonist investigated in clinical trials for the treatment of epilepsy by Novartis. Over the past decade, much attention has been given to 1-aminobenzimidazolones[5] which possess both valuable 4-phenylsemicabazide and benzimidazolone[6] skeletons (Figure 1). The compounds containing this motif are often biologically active: examples include antitumor[7a] and anti-inflammatory[7b] activities.

Figure 1. Representative bioactive compounds containing the 4-arylsemicabazide moiety.

Despite their potential applications in drug development, only limited approaches to 1-aminobenzimidazolones have been reported in the literature. The most commonly employed methods include carbonylation of 2-hydrazinylanilines,[5] Lewis acid mediated cyclization of diazenes,[8a,b] and amination[8c] of benzimidazolones (Scheme 1). The conventional strategies often suffered from multiple synthetic steps, a limited substrate scope, prefunctionalized starting materials, or required stoichiometric reagents. Thus, the development of a more efficient and straightforward approach to 1-aminobenzimidazolones is highly desirable.

For the construction of heterocycles possessing the N−N−C═O motif, nitrogen-substituted isocyanates (*N*-isocyanates)[9] are attractive functional precursors. Compared to normal isocyanates, the synthetic potential of *N*-isocyanates is rather underdeveloped, mainly due to the tendency of these amphoteric intermediates to dimerize.[9b] Recently, our group successfully implemented alkene aminocarbonylation[10] and several cascade reactions[1,11] of masked *N*-isocyanates[12] to afford diverse nitrogen heterocycles. This reactivity was enabled by the in situ generation of *N*-isocyanate intermediates from carbazates or carbazones. As part of these efforts, we speculated that masked *N*-isocyanates could be used as substrates for different sequences including metal-catalyzed reactions.

Scheme 1. Known Syntheses of 1-Aminobenzimidazolones



Interestingly, while cascade reactions involving isocyanates are common, metal-catalyzed variants are more scarce.[13] Examples using masked/blocked isocyanates are rare and have not been reported with *N*-isocyanates. On the other hand, cascade reactions involving copper catalyzed C−N bond formation[14] have attracted substantial attention because of their broad applicability and affordability. Therefore, we became interested in expanding the synthetic utility of *N*-isocyanates to copper catalyzed cascade reactions. Herein, we report the reaction of in situ generated *N*-isocyanates with 2-iodoanilines followed by Cu(I) catalyzed intramolecular

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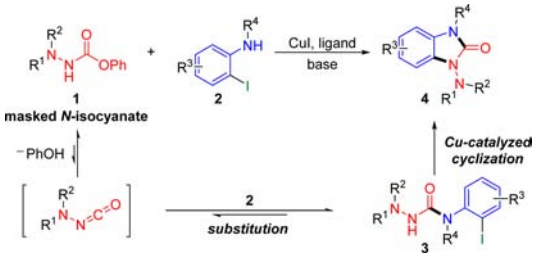
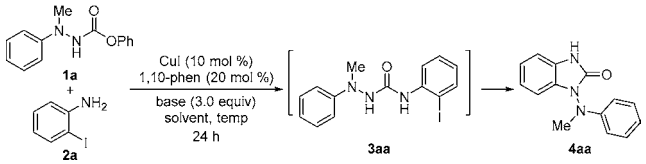
coupling to directly form functionalized 1-aminobenzimidazolones (Scheme 2).

Scheme 2. Reaction Design



The reaction, from a process optimization standpoint, needed to address challenges which included (1) the propensity of side reactions because of the somewhat reduced electrophilicity of amino-isocyanate intermediates and lower nucleophilicity of 2-iodoanilines and (2) the compatibility of *N*-isocyanate intermediates in the presence of a Cu(I) catalyst. Based on the optimization[15] of the intramolecular coupling reaction of semicarbazide intermediate **3aa**, *N*,*N*-disubstituted carbazate **1a** and 2-iodoaniline **2a** were chosen as substrates to test the cascade reaction in the presence of CuI (10 mol %) and 1,10-phenanthroline (20 mol %) (Table 1). However, when the optimal base for the intramolecular coupling was employed (K_2CO_3), the carbazide byproduct[16] rather than the desired 1-aminobenzimidazolone **4aa** was obtained (entry 1). By screening various bases, we were pleased to find that the utilization of DMAP could suppress the self-condensation of **1a** and the cascade reaction proceeded as envisioned affording the

Table 1. Optimization of the Reaction Conditions[a]



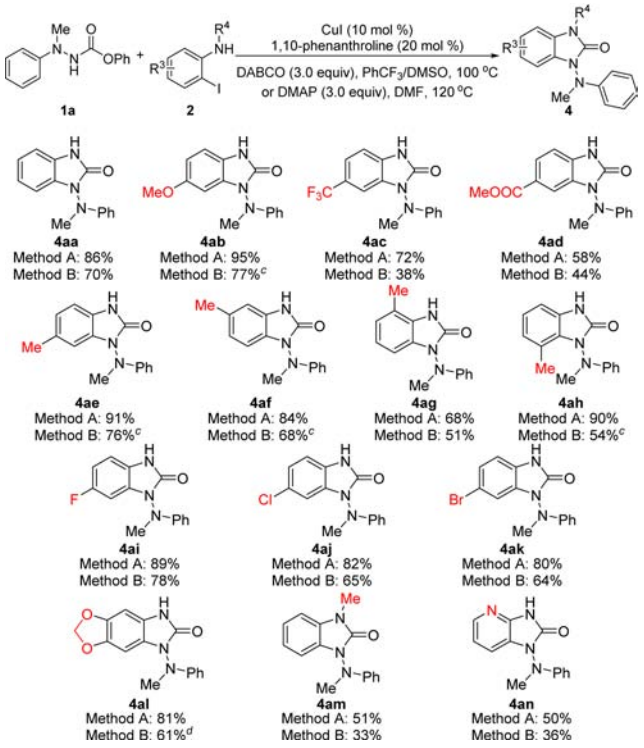
entry	base	solvent	temp (°C)	ratio (**1a**:**2a**)	yield (%)[b]
1	K_2CO_3	DMSO	100	1:1	trace
2	K_3PO_4	DMSO	100	1:1	trace
3	Et_3N	DMSO	100	1:1	trace
4	*i*-Pr_2NEt	DMSO	100	1:1	trace
5	DMAP	DMSO	100	1:1	59
6	DABCO	DMSO	100	1:1	50
7[c]	DMAP	MeCN	100	1:1	66
8	DMAP	DMF	120	1:1	66
9	DMAP	DMF	120	1:1.5	70
10	DMAP	DMF	120	1:2	70
11[c,d]	DMAP	DMF	120	1:1.5	0
12[e]	DMAP	$PhCF_3$/DMSO	100	1:1.5	73
13[e]	DABCO	$PhCF_3$/DMSO	100	1:1.5	86

[a]Conditions: **1a** (0.10 mmol), **2a** (0.10−0.20 mmol), CuI (0.01 mmol), 1,10-phenanthroline (0.02 mmol), base (0.30 mmol), solvent (1.0 mL). [b]Isolated yield. [c]The reaction was stirred at the indicated temperature for 48 h. [d]Without CuI and 1,10-phenanthroline. [e]Conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), base (0.30 mmol), $PhCF_3$ (1.0 mL), 100 °C, 24 h, and then concentrated; adding CuI (0.01 mmol), 1,10-phenanthroline (0.02 mmol), and DMSO (1.0 mL), then stirred at 100 °C for 12 h.

desired product **4aa** in 59% yield (entry 5). When the solvent was changed to MeCN, the yield of **4aa** increased to 66% although some intermediate **3aa** still remained even after 48 h at 100 °C (entry 7). Next, the cascade reaction was conducted in DMF at 120 °C in order to achieve complete conversion and the ratio of **1a** to **2a** was further examined. As expected, when this ratio was increased to 1:1.5, the desired product **4aa** was obtained in 70% yield (entry 9). A control experiment revealed that no cyclization product **4aa** formed when the CuI catalyst was omitted (entry 11). To improve the synthetic efficiency, the reaction of **1a** and **2a** was also investigated in a one-pot manner. To our delight, by performing the substitution step in $PhCF_3$ in the presence of DABCO and then concentrating *in vacuo*, followed by addition of CuI, 1,10-phenanthroline and DMSO gave the desired product **4aa** in 86% yield (entry 13). In the process of optimization, it was found that the substitution step was promoted by a catalytic amount of base.[15]

With the optimal reaction conditions in hand, a range of 2-iodoanilines were first examined (Scheme 3) to explore the

Scheme 3. Comparison of Efficiency of One-Pot Reaction and Cascade Reaction with 2-Iodoanilines[a,b]



[a]Conditions: Method A: **1a** (0.20 mmol), **2** (0.30 mmol), DABCO (0.60 mmol), $PhCF_3$ (2.0 mL), 100 °C, 12 h; concentrated; add CuI (0.02 mmol), 1,10-phenanthroline (0.04 mmol), DMSO (2.0 mL); 100 °C, 5 h; Method B: **1a** (0.20 mmol), **2** (0.30 mmol), DMAP (0.60 mmol), CuI (0.02 mmol), 1,10-phenanthroline (0.04 mmol), DMF (2.0 mL), 120 °C, 24 h. [b]Isolated yield. [c]Reaction time: 48 h. [d]Performed in DMSO at 100 °C.

substrate scope. As summarized in Scheme 3, the reaction displayed excellent tolerance for 2-iodoanilines, allowing a broad range of 1-aminobenzimidazolones to be obtained in moderate to excellent yields in both one-pot and cascade reaction conditions (methods A and B, respectively). The efficiency of the transformation was affected by electronic and steric effects of the substituents on the 2-iodoanilines. For

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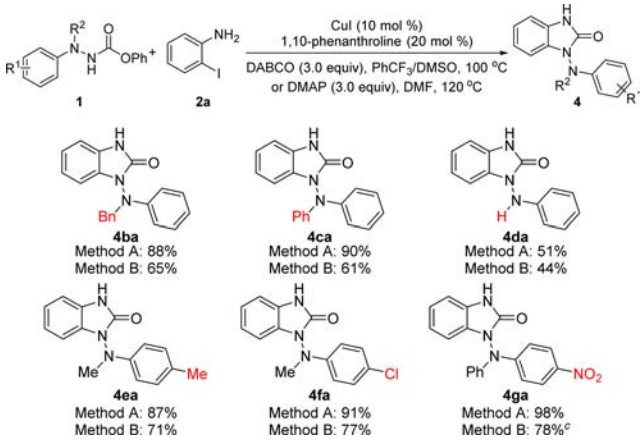
example, 2-iodo-4-methoxyaniline exhibited good reactivity and produced the corresponding product **4ab** in 95% yield (one-pot reaction) and 77% yield (cascade reaction). In contrast, 2-iodoanilines with electron-withdrawing groups gave slightly lower yields (**4ac** and **4ad**). This could be due to the decreased nucleophilicity of the anilines which allows irreversible formation of the self-condensation carbazide byproduct. As shown with substrates bearing methyl groups at different positions, more sterically hindered substrates such as 2-iodo-6-methylaniline resulted in a lower product yield (**4ag** vs **4ae**, **4af** and **4ah**). Of note, F, Cl, and Br substituents are well tolerated in this reaction and afforded the corresponding 1-amino-benzimidazolones (**4ai**, **4aj**, and **4ak**) in good yields, thereby providing the opportunity for subsequent coupling reactions. Moreover, the sterically demanding 2-iodo-*N*-methylaniline was successfully employed and furnished the desired product in moderate yield (**4am**). Importantly, the scope could be extended to incorporate heteroaryl substrates, although the reaction was less efficient. For instance, when 2-amino-3-iodopyridine was used, the corresponding heterocycle was obtained in 50% yield by the one-pot method (**4an**).

The scope of the reaction in terms of carbazates (**1**) was then investigated. As shown in Scheme 4, this substitution/

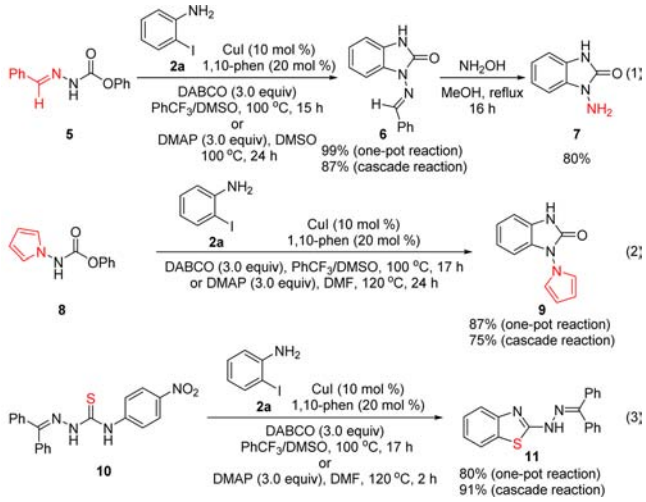
Scheme 4. Comparison of Efficiency of One-Pot Reaction and Cascade Reaction with Carbazates[a,b]



[a]Reaction conditions: Method A: **1** (0.20 mmol), **2a** (0.30 mmol), DABCO (0.60 mmol), $PhCF_3$ (2.0 mL), 100 °C, 12 h, then concentrated; adding CuI (0.02 mmol), 1,10-phenanthroline (0.04 mmol), DMSO (2.0 mL), 100 °C, 5 h; Method B: **1** (0.20 mmol), **2a** (0.30 mmol), DMAP (0.60 mmol), CuI (0.02 mmol), 1,10-phenanthroline (0.04 mmol), DMF (2.0 mL), 120 °C, 24 h. [b]Isolated yield. [c]The reaction was performed for 12 h.

cyclization process was general with respect to structural variations on the carbazate. When the *N*-substituent on the carbazate (**1**) was benzyl or phenyl, the reaction proceeded smoothly to provide the products in good yields (**4ba** and **4ca**). It is noteworthy that the parent *N*-H carbazate also participated in this transformation and afforded the corresponding product in moderate yield (**4da**). A nitro substituent was tolerated, and yields of 98% and 78% were obtained for the one-pot and cascade reactions, respectively (**4ga**). The electronic nature of the aryl ring did not have a significant impact on process efficiency (**4ea**–**4ga**), even if electron-withdrawing substituents appear beneficial, possibly by improving NH acidity.

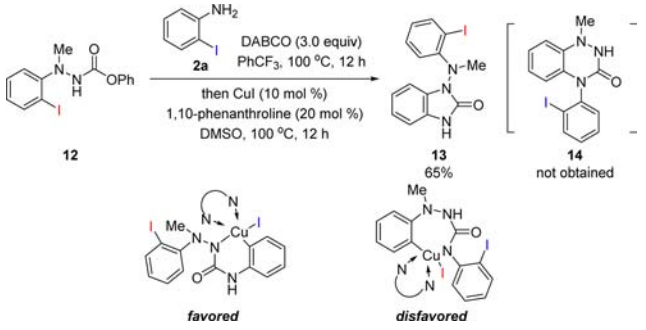
To expand the utility of this strategy, we turned our attention to other masked *N*-isocyanates. The aldehyde-derived hydrazone **5** showed higher reactivity than hydrazides. The reaction with substrate **5** proceeded efficiently to produce the corresponding product in excellent yield, which was followed by treatment with hydroxylamine to form the 1-amino-benzimidazolone **7** (eq 1). The masked *N*-isocyanate **8**



incorporating a pyrrole unit was also successfully employed in this reaction sequence, and the functionalized compound **9** was obtained in 87% yield (one-pot reaction) and 75% yield (cascade reaction) (eq 2). Furthermore, this cascade protocol could also be applied to the masked *N*-isothiocyanate substrate **10** to afford hydrazinylbenzo[*d*]thiazole **11** in 91% yield, which possesses a core structure exhibiting promising antioxidant activity[17] (eq 3).[18]

In order to clarify the mechanism of the coupling step,[19] iodo-substitued carbazate **12** was reacted with 2-iodoaniline **2a** under the optimal conditions. As illustrated in Scheme 5, the

Scheme 5. Cascade Substitution/Selective Cyclization Favored 1-Aminobenzimidazolone



five-membered 1-aminobenzimidazolone **13** was selectively formed rather than the six-membered heterocycle **14**. When the reaction time was prolonged, a trace amount of compound **4aa** was detected. Therefore, the possibility of a radical pathway can be excluded and an oxidative addition/reductive elimination mechanism is proposed for the intramolecular coupling reaction. The favored six-membered intermediate could account for the chemoselectivity observed with substrate **12**. Finally, while additional studies are needed to determine the mechanisms operating under the one-pot and cascade reactions

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conditions, the similarity of reactivity trends and reaction conditions support identical pathways.

In summary, a novel and efficient method for the elaboration of 1-aminobenzimidazolones through Cu(I)-catalyzed substitution/cyclization reactions of *N*-isocyanates has been developed. To our knowledge, this is the first metal-catalyzed cascade reaction with masked *N*-isocyanates. This method features simple experimental procedures, good functional group tolerance, and a broad substrate scope. The development of other metal catalyzed reaction sequences involving *N*-isocyanates is underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01686.

Additional optimization data, complete experimental procedures, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(18) When the reaction was performed in $PhCF_3$ at 100 °C for 16 h without CuI and 1,10-phenantroline, the cyclized product **11** could be obtained with 24% yield. The control in DMSO led to a 30% yield.

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