



Copper-catalyzed tandem reaction directed toward synthesis of 2,2-disubstituted quinazolinones from vinyl halides and 2-aminobenzamides



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ABSTRACT

A copper-catalyzed tandem reaction with vinyl halides and 2-aminobenzamides has been developed. In this synthetic route, cross-coupling reaction of the amide moiety with vinyl halides initially progresses, followed by hydroamination, to provide 2,2-disubstituted quinazolinone derivatives. Moreover, the tandem reaction is used in a one-pot synthesis beginning with alkyne hydroiodination by PPh₃, I₂, and H₂O.

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Introduction

Quinazolinone, an *N*-heterocyclic compound, is an important scaffold included in a great number of pharmacologically active compounds.¹ Therefore, development of convenient methods for the construction of quinazolinone structures is of great importance.² However, there are very few methods for the synthesis of 2,2-disubstituted quinazolinones as compared to those for other substituted quinazolinones.³ Condensation of 2-aminobenzamides with carbonyl compounds in the presence of acid catalysts is a simple and direct method to construct 2,2-disubstituted quinazolinones.⁴ Unfortunately, the substrate scope of this reaction is limited because the bulkiness of the substituents on the amino and ketone groups reduces the rate of the condensation reaction.⁵

We became interested in expanding methods for the synthesis of 2,2-disubstituted quinazolinones by developing tandem reactions. Tandem reactions have been a focus of great interest in this decade because they can streamline synthetic processes by reducing time, solvent, and waste.⁶ Our group has recently developed a convenient method to prepare vinyl iodides by hydroiodination of alkynes with PPh₃, I₂, and H₂O.⁷ Vinyl halides are considered to be

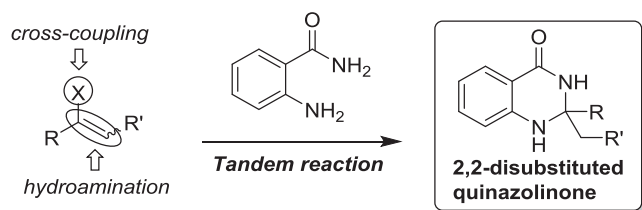
one of the most versatile building blocks for tandem reactions⁸ because they contain two reactive sites: the halogen group and the alkenyl group. Importantly, vinyl iodides are the most reactive among vinyl halides. Vinyl halides can be used for coupling reactions while the remaining vinyl groups can be used for addition reactions.

To exploit these features of vinyl halides, we designed a tandem reaction including cross-coupling and hydroamination: reaction of vinyl halides with 2-aminobenzamide to provide 2,2-disubstituted quinazolinone (Scheme 1). We assumed that the initial cross-coupling reaction of the amide moiety with the vinyl halide⁹ would trigger the subsequent hydroamination of the aromatic amine¹⁰ with intramolecular cyclization to afford 2,2-disubstituted quinazolinone. Herein, we wish to report a copper-catalyzed tandem reaction directed toward synthesis of 2,2-disubstituted quinazolinones from vinyl halides and 2-aminobenzamide.

In preliminary experiments, we selected 2-aminobenzamide **1a** and 2-iodooct-1-ene **2a** as model substrates (Table 1). The initial reactions were carried out in dioxane using CuI (20 mol%) as the catalyst, DMEDA (40 mol%) as a ligand, and Cs₂CO₃ (2 equiv) as a base at 110 °C. When 1 equiv of vinyl iodide **2a** was employed, the expected product **3a** was obtained in 51% yield (entry 1). The vinyl iodide was completely consumed, and no other by-product derived from 2-aminobenzamide was observed. When 2 equiv of vinyl iodide **2a** was used, the yield was dramatically increased to

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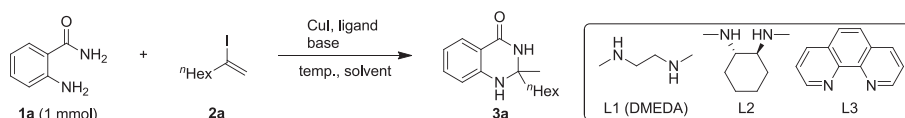
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Scheme 1. Tandem reaction of 2-aminobenzamide with vinyl halides to provide 2,2-disubstituted quinazolinones.

85% (entry 2). Decreased yields of **3a** were observed at lower temperatures (entries 3 and 4). When the amounts of CuI and DMEDA were decreased to 10 mol% and 20 mol%, respectively, similar reactivity was observed, although the reaction was prolonged from 21 h to 28 h (92%, entry 5). Increasing the amount of Cs₂CO₃ from 2 equiv to 3 equiv was also effective (93%, entry 6). When other bases such as K₂CO₃ and KO(*t*-Bu), which are often used with the copper catalyzed cross-coupling reaction of vinyl halides and aniline derivatives,^{9a,c} were employed, the yields were lowered (entries 7 and 8). The use of DMF and NMP resulted in lower

Table 1
Optimization of reaction conditions for the tandem reaction.



Entry	CuI (mol%)	Ligand (mol%)	Base (equiv)	Solvent	2a (equiv)	Temperature ^a	Time	Yield ^b
1	20	L1 (40)	Cs ₂ CO ₃ (2)	Dioxane	1	110 °C	21 h	51%
2	20	L1 (40)	Cs ₂ CO ₃ (2)	Dioxane	2	110 °C	21 h	85%
3	20	L1 (40)	Cs ₂ CO ₃ (2)	Dioxane	2	25 °C	19 h	Trace
4	20	L1 (40)	Cs ₂ CO ₃ (2)	Dioxane	2	60 °C	19 h	43%
5	10	L1 (20)	Cs ₂ CO ₃ (2)	Dioxane	2	110 °C	28 h	92%
6	10	L1 (20)	Cs ₂ CO ₃ (3)	Dioxane	2	110 °C	18 h	93%
7	10	L1 (20)	K ₂ CO ₃ (3)	Dioxane	2	110 °C	25 h	84%
8	10	L1 (20)	KO(<i>t</i> -Bu) (3)	Dioxane	2	110 °C	15 h	16%
9	10	L1 (20)	Cs ₂ CO ₃ (3)	DMF	2	110 °C	12 h	73%
10	10	L1 (20)	Cs ₂ CO ₃ (3)	NMP	2	110 °C	12 h	59%
11	10	L2 (20)	Cs ₂ CO ₃ (3)	Dioxane	2	110 °C	13 h	93%
12	10	L3 (20)	Cs ₂ CO ₃ (3)	Dioxane	2	110 °C	22 h	81%
13	10	None	Cs ₂ CO ₃ (3)	Dioxane	2	110 °C	24 h	59%
14	None	None	Cs ₂ CO ₃ (3)	Dioxane	2	110 °C	22 h	0%

^a Bath temperature.

^b Determined by HPLC.

Table 2
Substrate scope of copper-catalyzed tandem reaction of 2-aminobenzamide with vinyl halides.

Entry	2-Aminobenzamide	Vinyl halide	Time	Product	Yield ^a
1 ^b	1a	Hex ⁿ 2a	18 h	3a	92% (83%)
2 ^b	1a	ⁿ Pr 2b	24 h	3b	89% (81%)
3 ^b	1a	2c	22 h	3c	92% (89%)
4 ^b	1a	2d	16 h	3d	95% (93%)
5 ^b	1b	Hex ⁿ 2a	32 h	3e	72% (69%)

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