ORGANIC LETTERS

2009
Vol. 11, No. 11
2469−2472

An Efficient One-Pot Copper-Catalyzed Approach to Isoquinolin-1(2*H*)-one Derivatives

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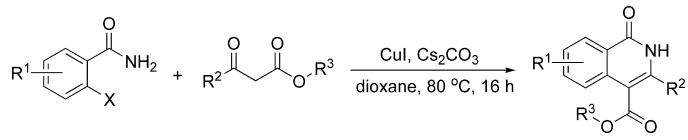
Received April 9, 2009

ABSTRACT



A simple and efficient copper-catalyzed method for synthesis of 3,4-disubstituted isoquinolin-1(2*H*)-one derivatives via cascade reactions of substituted 2-halobenzamides with *β*-keto esters under mild conditions has been developed, and the method has economical and practical advantages.

Isoquinolin-1(2*H*)-one derivatives are found in natural products such as thalifoline,[1] dorianine,[2] ruprechstyril,[3] narciclasine,[4] pancratistatin,[4] and lycoricidine[4b] in Figure 1, and they are also versatile building blocks for the total synthesis of natural alkaloids.[5] Substituted isoquinolin-1(2*H*)-ones exhibit various biological and medicinal activities such as antihypertensive activity[6a,b] and function as NK3 antagonists,[6c] melatonin MT_1 and MT_2 receptor agonists,[6d] Rho-kinase inhibitors,[6e] and JNK inhibitors.[6f] Some of them are also used as novel orally active 5-HT3 antagonists[7a] and thymidylate synthase (TS) inhibitors[7b] or for the treatment of stomach tumors and diseases of human brain cells.[2] Some approaches to isoquinolin-1(2*H*)-one derivatives have been developed, such as the rearrangement of 2-(2-benzofuranyl)-benzonitriles,[8] base-promoted condensation of 2-(bromomethyl)benzonitrile,[9] transformation of isocoumarins or 3-hydroxyphthalides,[10] double metalation of arylbenza-

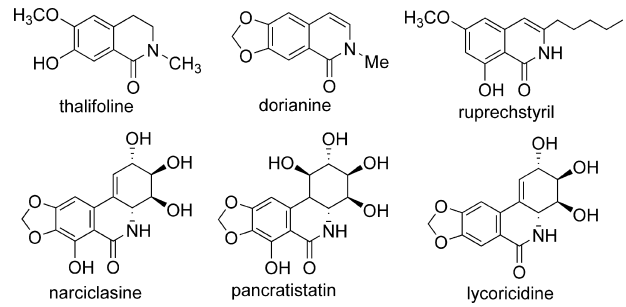


Figure 1. Isoquinolin-1(2*H*)-one derivatives of related natural products.

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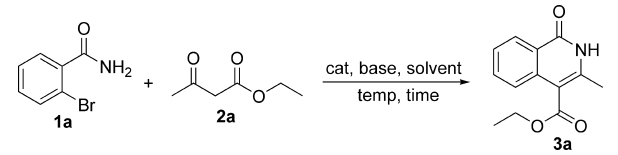
10.1021/ol900847t CCC: $40.75
Published on Web 05/07/2009

mides,[11] the cyclization of 2-chlorobenzonitriles with β-keto esters,[12] intramolecular Diels−Alder reactions,[13] Wittig reactions,[14] as well as photochemical reactions.[6b,15] Although these methods are effective, some starting materials are not readily available or are difficult to prepare. Recently, transition-metal-based catalysis has often been utilized for the synthesis of various heterocyclic compounds;[16] however, only limited examples applicable to the synthesis of isoquinolin-1(2*H*)-ones have appeared.[17] Recently, great progress for copper-catalyzed Ullmann couplings have been made,[18] and we have also developed some copper-catalyst systems that were used in *N*-arylations.[19] Some *N*-heterocycles have been constructed via the Ullmann couplings by us[20] and other research groups.[21] Herein, we report an efficient one-pot copper-catalyzed approach to isoquinolin-1(2*H*)-one derivatives via cascade reactions of *o*-halobenzamides with β-keto esters under mild conditions.

As shown in Table 1, 2-bromobenzamide (**1a**) and ethyl acetoacetate (**2a**) were chosen as the model substrates to optimize reaction conditions including catalysts, bases, solvents, and temperature. First, the reaction temperature was investigated by using 0.1 equiv of CuI as the catalyst and 2 equiv of Cs_2CO_3 as the base (relative to amount of **1a**) in dioxane (entries 1−3). The yield of the target product was greatly improved as the reaction temperature was increased, and higher yields were provided at more than 80 °C (entries 2 and 3). The coupling efficiency was evidently decreased in the absence of catalyst (entry 4), and only a trace amount of product was observed without addition of base (entry 5). The yield of target product decreased and byproduct increased in the absence of nitrogen atmosphere (entry 6). Other bases, K_3PO_4 and K_2CO_3, were screened at 80 °C (entries 7 and 8), and the results showed that Cs_2CO_3 provided the highest yield (entry 2). Sodium ethoxide was also an effective base in ethanol (entry 9). The effect of solvent was investigated (entries 2 and 9−11), and toluene

Table 1. Copper-Catalyzed Coupling of 2-Bromobenzamide with Ethyl Acetoacetate: Optimization of the Reaction Conditions[a]



entry	catalyst	base	solvent	temp /time	yield (%)[b]
1	CuI	Cs_2CO_3	dioxane	25 °C/16 h	trace
2	**CuI**	**Cs_2CO_3**	**dioxane**	80 °C/16 h	**80**
3	CuI	Cs_2CO_3	dioxane	120 °C/16 h	82
4	−	Cs_2CO_3	dioxane	80 °C /36 h	33
5	CuI	−	dioxane	80 °C/16 h	trace
6	CuI	Cs_2CO_3	dioxane	80 °C/16 h	29[c]
7	CuI	K_3PO_4	dioxane	80 °C/16 h	67
8	CuI	K_2CO_3	dioxane	80 °C/16 h	51
9	CuI	NaOEt	ethanol	80 °C/16 h	72
10	CuI	Cs_2CO_3	toluene	80 °C/16 h	63
11	CuI	Cs_2CO_3	DMF	80 °C/16 h	79
12	CuBr	Cs_2CO_3	dioxane	80 °C/16 h	76
13	$CuCl_2$	Cs_2CO_3	dioxane	80 °C/16 h	38

[a] Reaction conditions: nitrogen atmosphere, 2-bromobenzamide (0.5 mmol), ethyl acetoacetate (0.75 mmol), catalyst (0.05 mmol), base (1 mmol), solvent (3 mL). [b] Isolated yield. [c] In the absence of nitrogen atmosphere.

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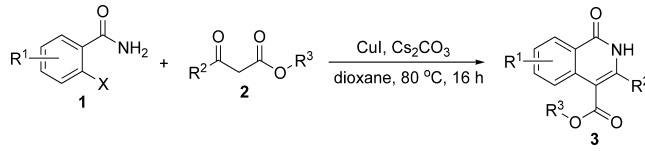
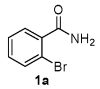
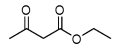
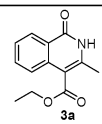
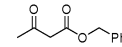
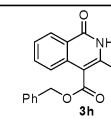
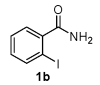
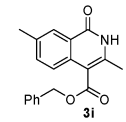
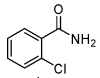
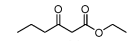
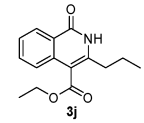
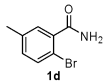
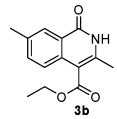
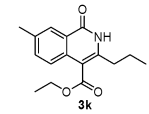
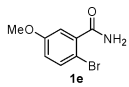
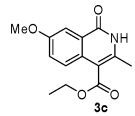
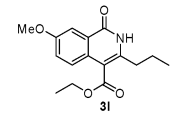
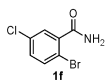
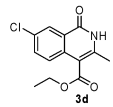
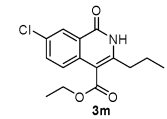
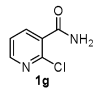
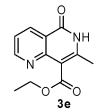
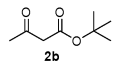
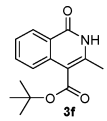
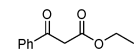
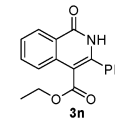
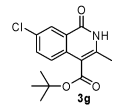
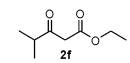
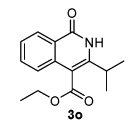
Table 2. Copper-Catalyzed Synthesis of Isoquinolin-1(*2H*)-one Derivatives[a]



entry	1	2	product (**3**)	yield (%)[b]	entry	1	2	product (**3**)	yield (%)[b]
1				80	10	**1a**			76
2		**2a**	**3a**	83	11	**1d**	**2c**		65
3		**2a**	**3a**	35	12	**1a**			76
4		**2a**		86	13	**1d**	**2d**		75
5		**2a**		70	14	**1e**	**2d**		53
6		**2a**		62	15	**1f**	**2d**		81
7		**2a**		60	15	**1f**	**2d**		81
8	**1a**			83	16	**1a**			51
9	**1f**	**2b**		63	17	**1a**			32

[a] Reaction conditions: nitrogen atmosphere, 2-halobenzamide (1 mmol), β-keto ester (1.5 mmol), CuI (0.1 mmol), Cs_2CO_3 (2 mmol), dioxane (5 mL). [b] Isolated yield.

and DMF provided slightly lower yields (entries 10 and 11). Several copper salts were also tested (compare entries 2, 12, and 13), and CuI was proven to be the most effective catalyst (entry 2).

The scope of copper-catalyzed coupling reactions of substituted 2-halobenzamides with β-keto esters was investigated under the optimized conditions (10 mol % CuI as the catalyst, 2 equiv of Cs_2CO_3 as the base, dioxane as the solvent at 80 °C under nitrogen atmosphere). As shown in Table 2, most of the substrates examined provided good yields. For the substituted 2-halobenzamides, their relative reactivity was in the order of aryl iodides > aryl bromides > aryl chlorides. Reaction of 2-chloronicotinamide with ethyl acetoacetate also provided the target product **3e** in moderate yield (60%). For β-keto esters, the steric hindrance is a key factor, and the β-keto esters containing bigger groups such as phenyl (entry 16), isopropyl (entry 17) provided lower yields. The reactions above did not need addition of any ligand or additive. Interestingly, nucleophilic attack of amino group only occurred on the ketone rather than on ester of β-keto ester. In addition, the cascade reactions could tolerate some functional groups such as ester, C−Cl bond (entries 6, 9, and 15).

In summary, we have developed a simple and highly efficient method for synthesis of 3,4-disubstituted isoquinolin-1(2*H*)-one derivatives. The couplings of 2-bromo- and -iodobenzamides or 2-chloronicotinamide with β-keto esters were performed well at 80 °C without addition of any ligand

or additive. The present method shows economical and practical advantages over the previous methods and uses a readily available starting material, so it will provide a new strategy for construction of diverse and useful isoquinolin-1(2*H*)-one derivatives in organic chemistry and medicinal chemistry.

Acknowledgment. This work was supported by the National Natural Science Foundation of China (Grant No. 20672065, 20732004), Chinese 863 Project (Grant No. 2007AA02Z160, 2006DFA43030). Programs for New Century Excellent Talents in University (NCET-05-0062) and Changjiang Scholars and Innovative Research Team in University (PCSIRT) (No. IRT0404) in China, and the Key Subject Foundation from Beijing Department of Education (XK100030514).

Supporting Information Available: Synthetic procedures, characterization data, and ^{1}H, ^{13}C NMR spectra of these synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900847T