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Synthesis of 3*H*-naphtho[2.1-*b*]pyran-2-carboxamides from cyclocoupling of β-naphthol, propargyl alcohols and isocyanide in the presence of Lewis acids

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ABSTRACT

3*H*-Naphtho[2.1-*b*]pyran-2-carboxamides (3*H*-Benzo[*f*]chromene-2-carboxamides) can be synthesized from a three-component cyclocoupling reaction of β-naphthol, propargyl alcohols and isocyanide in the presence of ZnI_2 and $FeCl_3$ under air atmosphere. The reaction is proposed to involve the formation of aryl-zinc (II) σ-bond and its α-addition to isocyanide.

1. Introduction

2*H*-Chromene and 3*H*-naphtho[2.1-*b*]pyran are important *O*-heterocyclic motifs, which are well found in both natural products and synthesized molecules possessing interesting biological and physiological properties (Scheme 1, **I** and **II**).[1] In addition, it has been well-known that amide moiety is the key component in some biomolecules and drugs.[2] 3*H*-Naphtho[2.1-*b*]pyran-2-carboxamides (Scheme 1, **III**), incorporating above-mentioned *O*-heterocyclic motifs and α, β-unsaturated amide group, are expected to be an ideal and interesting scaffold for the future studies in developing bioactive molecules.

On the other hand, propargyl alcohols have been well used as the versatile synthons in the syntheses of various *O*-heterocycles *via* their cyclocondensation,[3] 3,3-diaryl-3*H*-naphtho[2,1-*b*]pyran,[4] 3,3-dimethyl-3*H*-naphtho[2,1-*b*]pyran[5] could be prepared from a *p*-TsOH- or $ReCl(CO)_5$-catalyzed cyclocondensation of 1,1-diaryl-2-propyn-1-ol or 2-methyl-3-butyn-2-ol with β-naphthol, respectively (Scheme 2a). As a continuation of our interest in synthesis of heterocyclic compounds from annulations protocols of alkyne[6] and propargyl compounds,[5,7] as well as Zn(II) salts have been well-applied as the versatile catalysts in the synthesis of heterocyclic compounds,[8] we therefore report here a three-component cyclocoupling reaction of β-naphthol, propargyl alcohols and cyclohexyl isocyanide in the presence of ZnI_2 and $FeCl_3$ affording 3*H*-naphtho[2.1-*b*]pyran-2-carboxamides (Scheme 2b).

2. Results and discussion

When a mixture of β-naphthol (**1a**), 2-methyl-4-phenyl-3-butyn-2-ol (**2a**, 1.3 equiv), cyclohexylisocyanide (**3a**, 2.0 equiv), $ZnCl_2$ (0.1 equiv) and K_3PO_4 (1.0 equiv) in toluene was stirred at 80 °C for 7 h under air, the cyclocoupling product of 3*H*-naphtho[2.1-*b*]pyran-2-carboxamide derivative (**4aa**) was obtained in 23% isolated yield (Table 1, entry 1), the use of Cs_2CO_3 or CsF, instead of K_3PO_4 resulted in an increase of yields (Table 1, entries 2–3). In the case of ZnI_2 and CsF used, **4aa** could be obtained in 50% yield (Table 1, entry 4). A combined use of ZnI_2 and $FeCl_3$ as the catalyst system, **4aa** formed in 67–79% yields (Table 1, entries 5–7). Under the similar reaction conditions as indicated entry 7, the yield of **4aa** was greatly decreased with the decease of reaction temperature (60 °C, 55%), and the yield could not be improved with a higher reaction temperature (100 °C). As shown in entries 8–11, the solvent effect is

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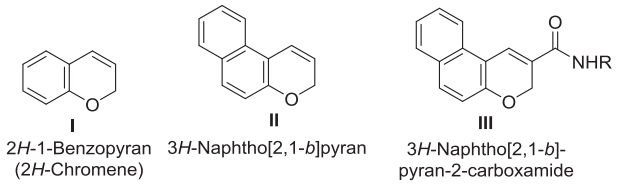
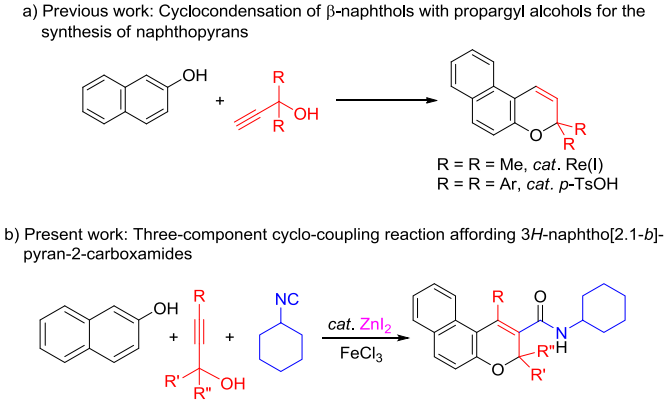


Scheme 1. Structures of 2*H*-1-benzopyran, 3*H*-naphtho[2.1-*b*]pyran and 3*H*-naphtho-[2.1-*b*]pyran-2-carboxamide.



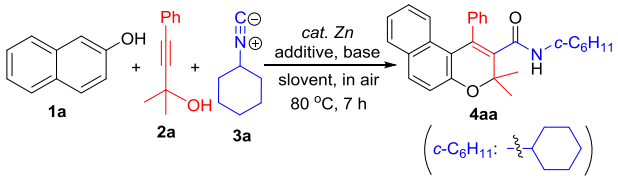
Scheme 2. Synthesis of naphthopyrans *via* cyclocondensation of β-naphthols and propargyl alcohols.

desired 3*H*-naphtho[2.1-*b*]pyran-2-carboxamides in good to high yields. In the case of 4-aryl-2-methyl-3-butyn-2-ols employed, the aryl groups having electron-donating group at *para*-position show the similar reactivity as phenyl group to give the corresponding cyclocoupling products (**4ab**~**4ae**) in good yields. 2-methyl-4-(2-thienyl)-3-butyn-2-ol, a thienyl-substituted propargyl alcohol also undergoes the cyclocoupling reaction to give the expected product (**4af**) in 61% yield. Noted that a slight electron effect was observed by using different aryl groups directly bonded to the terminal carbon of propargyl alcohols. 4-Aryl-2-methyl-3-butyn-2-ols bearing the electron-deficient aryl groups such as *p*-FC_6H_4, *p*-ClC_6H_4 and *p*-NCC_6H_4 show higher reactivity to produce the expected products (**4ag**~**4ai**) in the higher yields.

The propargyl alcohols with a phenyl group at the carbon of alcohol (1-aryl-3-phenyl-1-butyn-3-ol) shows higher reactivity to afford the corresponding cyclocoupling products (**4aj**~**4al**) in high to excellent yields. The high reactivity may be due to the high electrophilicity of allenyl carbocation intermediate in the electrophilic substitution reaction with naphthyl ring as shown in the proposed mechanism (*vide infra*). Thus in the cases of 1-aryl-3-methyl-1-nonyn-3-ol employed, propargyl alcohols having two alkyl groups at the carbon of alcohol, the cyclocoupling reactions gave the products (**4am** & **4an**) in 71% and 78% yields.

In addition, cyclohexyl propargyl alcohols such as 1-(2-phenylethynyl)-cyclohexanol and 1-[2-(4-fluorophenyl)ethynyl]-cyclohexanol also show the good reactivity to undergo the cyclocoupling reactions with **1a** and **3a** to afford the corresponding

Table 1
Optimization of the reaction conditions.[a]



Entry	Catalyst (mol%)	Additive (mol%)	Base (1.0 equiv)	Solvent	Yield (%)[b]
1	$ZnCl_2$ (10)	–	K_3PO_4	toluene	23
2	$ZnCl_2$ (10)	–	Cs_2CO_3	toluene	30
3	$ZnCl_2$ (10)	–	CsF	toluene	39
4	ZnI_2 (10)	–	CsF	toluene	50
5	ZnI_2 (10)	$FeCl_3$ (10)	CsF	toluene	67
6	ZnI_2 (15)	$FeCl_3$ (10)	CsF	toluene	77
7[c]	**ZnI_2 (15)**	**$FeCl_3$ (5)**	**CsF**	**toluene**	**79**
8	ZnI_2 (15)	$FeCl_3$ (10)	CsF	MeCN	43
9	ZnI_2 (15)	$FeCl_3$ (10)	CsF	CH_2Cl_2	NR
10	ZnI_2 (15)	$FeCl_3$ (10)	CsF	dioxane	NR
11	ZnI_2 (15)	$FeCl_3$ (10)	CsF	DMF	NR
12	–	$FeCl_3$ (10)	CsF	toluene	NR

[a] Reactions were carried out using **1a** (1.0 mmol), **2a** (1.3 mmol), **3a** (2.0 mmol) in 10 mL of solvent.
[b] Isolated yields based on the amount of **1a**.
[c] **4aa** was obtained in 55% yield, when the reaction was performed at 60 °C.

apparent for the present cyclocoupling reaction, when MeCN, CH_2Cl_2, 1,4-dioxane and DMF were used as solvents, **4aa** either was produced in low yield, or could not form at all. In addition, the reaction could not give **4aa** without ZnI_2 (Table 1, entry 12).

Under the reaction conditions indicated in entry 7 of Table 1, the scope of the reaction substrates has been investigated, and the representative results are summarized in Table 2. The three-component cyclocoupling reactions of **1a** and **3a** with a variety of propargyl alcohols bearing various substituents can afford the products **4ao** and **4ap** in 69% and 72% yield, respectively.

Attempted reactions using either 2-methyl-3-butyn-2-ol (a terminal propargyl alcohol), or other isocyanides such as *t*-butylisocyanide and isopropylisocyanide gave none of the desired products, and the reactions gave a mixture of unidentified by-product. The use of α-naphthol could not obtain the desired product either.

On the basis of the present transformation and the well-known chemistry of isocyanide insertion to metal-carbon σ-bond,[9] and zinc-carbon bond,[10] a proposed mechanism for the formation of