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One-pot facile synthesis of polysubstituted pyridines via tandem reaction of the Blaise reaction intermediates and 3-formylchromones

Zhiwei Chen[a]*, Zhaoran Dai[a], Zhangxia Zhu[a] and XiaoFeng Yang[a]

[a] *Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou, 310014, P. R. China; College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou, 310014, P. R. China*

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ABSTRACT

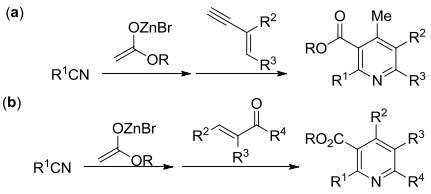
A novel tandem one-pot method for the synthesis of polysubstituted pyridine derivatives has been developed via Knoevenagel-type reaction and subsequent 6π electrocyclization of the Blaise reaction intermediates and 3-formylchromones. Short reaction time, moderate to good yields and excellent functional group tolerance have been accomplished in this protocol.

Of the *N*-heterocycles, pyridines are among the most prevalent scaffolds which are not only present in natural products, but are also widely used in functional materials, pharmaceuticals and synthetic intermediates[1]. Due to their importance, a large amount of synthetic methods have been developed for the preparation of pyridines and its derivatives. Classical methods for the synthesis of polysubstituted pyridines includes Hantzsch reaction[2], Krohnke reaction[3], Aza-Diels-Alder reaction[4]. In addition to those divergent strategies, modification of pre-existing pyridine frameworks via metal-catalyzed cross-coupling reaction to afford polysubstituted target products is also well developed[5]. Although pyridines could be generated efficiently under the above reaction conditions, difficulties arised from the preparation of starting materials, long reaction time or expensive catalysts can preclude their extensive application. Therefore, novel complementary approaches to densely substituted pyridines still remains as a hot research topic.

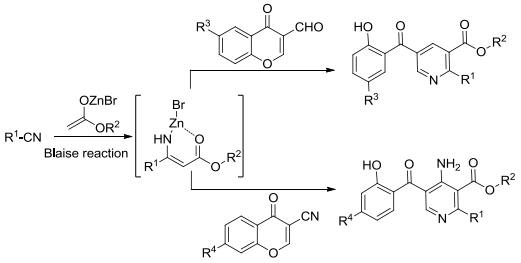
The classic reaction of zinc-mediated transformation of nitriles and ethyl bromoacetate, known as the Blaise reaction[6], has long been prepared corresponding β-ketoesters and β-enaminoesters[7]. In recent years, the Blaise reaction intermediates have been trapped with suitable building blocks in a tandem manner, which provided facile access to a great number of heterocyclic compounds[8]. In this regard, Lee and co-workers have developed an efficient protocol for the synthesis of polysubstituted pyridines through a tandem one-pot reaction using the Blaise reaction intermediates and 1,3-enynes[9] (Scheme 1a). In order to overcame the limitation of their previous procedure, an update of this method has been reported recently allowing diverse substitutes to be installed at the 4-position of the pyridine rings[10] (Scheme 1b).

It is well known that 3-formylchromone possessing a very reactive electrophilic center at C-2, a conjugated second carbonyl group at C-3 and an unsaturated keto function[11], have been used as an important synthetic building blocks to prepare heterocyclic compounds.

Previous work by Lee and co-works



This work



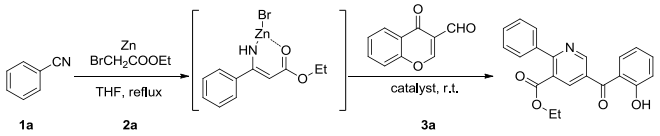
Scheme 1. Synthesis of polysubstituted pyridines via tandem reaction.

* Corresponding author. Tel. (fax): +86 571 88871087; e-mail: chenzhiwei@zjut.edu.cn

Based on the previous works as well as our continuous interests on the development of multicomponent heterocyclic chemistry[12], we envisioned the one-pot method for the feasible synthesis of polysubstituted pyridine derivatives via tandem reaction of the Blaise reaction intermediates and 3-formylchromones.

Table 1

Optimization of the reaction conditions[a]



1a 2a 3a

Entry	Catalysts	Loading (mol%)	Solvents	Yield(%)
1	-	-	THF	70
2	-	-	DCE	60
3	-	-	1,4-dioxane	67
4	$Cu(OTf)_2$	20	THF	70
5	$Cu(OTf)_2$	50	THF	68
6	$Yb(OTf)_3$	20	THF	65
7	$Zn(OTf)_2$	20	THF	62
8	$ZnCl_2$	20	THF	69
9	$CuCl_2$	20	THF	68
10	$AlCl_3$	20	THF	58
11	$BF_3{\cdot}Et_2O$	20	THF	63
12	$MeSO_3H$	20	THF	59
13	PTSA	20	THF	55

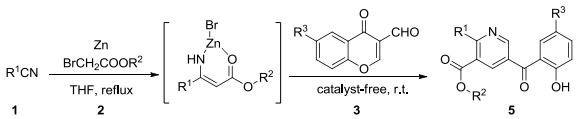
[a] All reactions were carried out with benzonitrile (1 mmol), zinc (2 mmol) and ethyl bromoacetate (1.5 mmol) in THF at reflux for 1 h, 3-formylchromone (1.5 mmol) was then added at r.t..

[b] Isolated yields based on benzonitrile.

To check our hypothesis, we initially performed a model reaction between 3-formylchromone (2.0 equiv) and the Blaise reaction intermediate which was formed from the reaction between benzonitrile and a Reformatsky reagent generated *in situ* from ethyl bromoacetate (1.5 equiv) and zinc powder (2.0 equiv) in THF. To our delight, the expected product ethyl 5-(2-hydroxybenzoyl)-2-phenylnicotinate **5a** was obtained in 70% yield (Table 1, entry 1). Then, screening of the solvents in this reaction revealed that THF was better than DCE and 1,4-dioxane in regards of yield. Thus, THF was the most suitable solvent due to the stablization of THF imposed on zinc complex[13]. With the optimal solvent in hand, diverse Lewis acids and protic acids were investigated for the tandem reaction in THF. Among them, $Cu(OTf)_2$, $Yb(OTf)_3$, $Zn(OTf)_2$, $ZnCl_2$, $CuCl_2$, $AlCl_3$, $BF_3{\cdot}Et_2O$, $MeSO_3H$ and PTSA showed moderate reactivity and there was no effect to promote the reaction. Consequently, the second step of the tandem reaction was perfomed without any additive.

Table 2

Synthesis of various substituted pyridine derivatives [a]



1 2 3 5

Entry	R^1	R^2	R^3	Product	Yield(%)[b]	Entry	R^1	R^2	R^3	Product	Yield(%)[b]
1	C_6H_5	Et	H	**5a**	70	10	2-MeC_6H_4	*t*-Bu	H	**5j**	71
2	C_6H_5	Me	H	**5b**	68	11	2-(*p*-tolyl)C_6H_4	*t*-Bu	H	**5k**	53
3	C_6H_5	*t*-Bu	H	**5c**	73	12	$C_6H_5CH_2$	*t*-Bu	H	**5l**	65
4	4-MeC_6H_4	*t*-Bu	H	**5d**	69	13	4-$ClC_6H_4CH_2$	*t*-Bu	H	**5m**	63
5	4-$MeOC_6H_4$	*t*-Bu	H	**5e**	66	14	CH_3	*t*-Bu	H	**5n**	59
6	4-$CF_3C_6H_4$	*t*-Bu	H	**5f**	79	15	$CH_3(CH_2)_3$	*t*-Bu	H	**5o**	55
7	4-ClC_6H_4	*t*-Bu	H	**5g**	75	16	Cyclopropyl	*t*-Bu	H	**5p**	60
8	4-FC_6H_4	*t*-Bu	H	**5h**	77	17	C_6H_5	*t*-Bu	Me	**5q**	69
9	2-ClC_6H_4	*t*-Bu	H	**5i**	67	18	C_6H_5	*t*-Bu	Br	**5r**	72

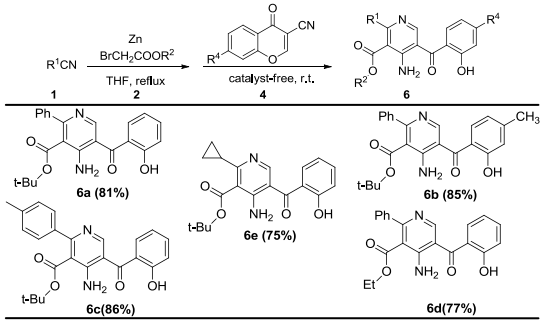
[a] All reactions were carried out with nitrile **1** (1 mmol), zinc (2 mmol) and bromoacetic ester **2** (1.5 mmol) in THF at reflux for 1 h, 3-formylchromone **3** (1.5 mmol) was then added at r.t.. [b] Isolated yields based on nitrile **1.**

Under the optimized reaction conditions, we next explored the scope and limitation of the reaction. As shown in Table 2, the examined substrates provided moderate to good yields. In early experiments, for the substituted R^2, *ter*-butyl in place of methyl or ethyl resulted in a slight increasement of yields (entries 1-3, Table 2). This results indicating that the steric bulk of the bromoacetic ester was favorable in the process which may decrease the side product formed from the attack of Reformatsky to the -$COOR^2$ group. For the substituted R^1, readily available aryl nitriles substituted with electron-withdrawing groups such as 2-Cl, 4-Cl, 4-F and 4-CF_3 offered high yields of tandem products (entries 6-9 Table 2). On the other hand, reactions involving aryl nitriles with electron rich substituents produced desired pyridines in slight lower yields (entries 4-5, Table 2). In addition, due to the steric hindrance of the substitutes on the aryl groups, the aryl nitriles bearing *ortho*-substituted group gave rise to products in lower yield than *para*-substituted nitriles. Especially, 2-(4-methylphenyl)benzonitrile with large steric bulk participated in the tandem raction to afford a few desired pyridine (entry 11, Table 2). To our delight, the Blaise intermediates, prepared form aliphatic nitriles (entries 12-16, Table 2), reacted smoothly under the optimized conditions to give the corresponding tandem products. However, acetonitrile, pentanenitrile and cyclopropanecarbonitrile were carried out in the poor performance towards the generation of the corresponding products. For the substituted R^3, 3-formylchromone substituted with 6-CH_3 and 6-Br also showed good reactivity(entry 17-18, Table 2).

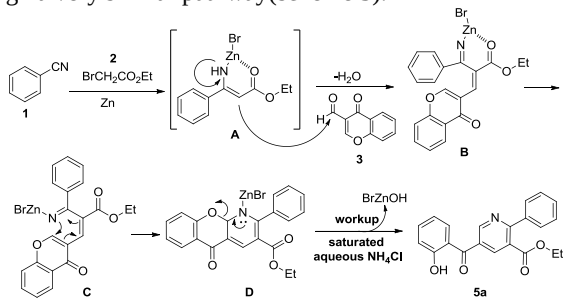
Moreover, these initial findings encouraged us to extend this methodology to other substrates. As shown in Table 3, the tandem reaction of the Blaise intermediates and 3-cyanochromones were carried out under the standard reaction conditions to afford more complex and diverse products, which could introduce a amino group at the 4-position of the pyridine ring in a convenient manner. Overall, the combination of the Blaise intermediates and 3-cyanochromones afforded the corresponding polysubstituted pyridine derivatives in 75-86% yields.

Table 3

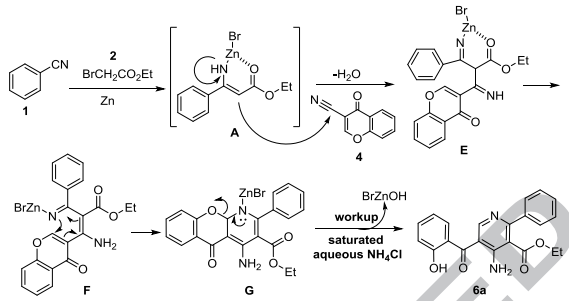
Synthesis of 4-NH_2 substituted pyridine derivatives.



Based on the above observations and previous reports[9, 14], a plausible pathway for the formation of ethyl 5-(2-hydroxybenzoyl)-2-phenylnicotinate **5a** is proposed in scheme 2. Initially, a zinc-mediated Blaise reaction between benzonitrile **1** and ethyl bromoacetate **2** takes place to give an enamino ester intermediate **A**. Secondly, intermediate **B** is afforded through Knoevenagel-type reaction of the Blaise intermediate **A** and 3-formylchromone **3**, Then, intermediate **B** undergoes a subsequent intramolecular transformation to produce N-zincated intermediate **C**, which could facilitate a 6π electrocyclization to afford intermediate **D**. Finally, the product **5a** is given via C–O bond cleavage and elimination of BrZnOH after workup. Accordingly, 3-cyanochromone participates the tandem reaction through a very similar pathway(scheme 3).



Scheme 2. Proposed mechanism of the reaction of 3-formylchromone



Scheme 3. Proposed mechanism of the reaction of 3-cyanochromone

In summary, we have described a novel divergent one-pot method for the synthesis of polysubstituted pyridine derivatives from easily accessible starting materials. This tandem reaction proceeds through the regio- and chemoselective Knoevenagel-type reaction between the Blaise reaction intermediates and 3-formylchromones, followed by an intramolecular cyclization to afford target products. Furthermore, We have extended the applications of the present method using 3-cyanochromones as substrates to introduce amino group at the pyridine core in a feasible pathway.

Acknowledgments

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15. Typical procedure for the synthesis of polysubstituted pyridine derivative: To a stirred suspension of commercial zinc dust (2.0 mmol) in anhydrous THF (3.0 mL) was added a solution of $MeSO_3H$ in THF (1.0 M, 0.2 mL) at 80°C (oil bath). After stirring for 10 min, benzonitrile **1** (1.0 mmol) and ethyl bromoacetate **2** (1.5 mmol) was added over 1 h, and then the reaction mixture was further stirred at reflux for 1 h. After confirmed conversion of benzonitrile **1** (>95%) to the Blaise reaction intermediate **A** by gas chromatography, the reaction mixture was cooled to room temperature, and then 3-formylchromone **3** (1.5 mmol) was added. Upon completion of the reaction, aqueous NH_4Cl (10 mL) was added and the excess zinc was filtered. The filtrate was concentrated and water (5 mL) was added to the residue. The solution was extracted with EtOAc (3 x 10 mL). The organic phases were combined, dried with anhydrous Na_2SO_4 and then concentrated. The residue was purified by column chromatography (EtOAc/hexane, 1:10 v/v) to afford product **5a**. Yield: (243 mg, 70%); Characteristic: pale yellow powder; Mp 89-91°C (Lit.[11b]: 80-90°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.78 (s, 1H), 9.03 (d, *J* = 2.0 Hz, 1H), 8.40 (d, *J* = 2.0 Hz, 1H), 7.65-7.53 (m, 4H), 7.51-7.41 (m, 3H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 1.09 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.72, 166.95, 163.15, 160.95, 150.48, 139.08, 138.20, 136.89, 132.65, 131.28, 129.22, 128.63, 128.06, 127.12, 119.03, 118.92, 118.69, 61.85, 13.74. MS (ESI): m/z = 348 $[M+H]^+$.

Graphical Abstract.

One-pot facile synthesis of polysubstituted pyridines via tandem reaction of the Blaise reaction intermediates and 3-formylchromones

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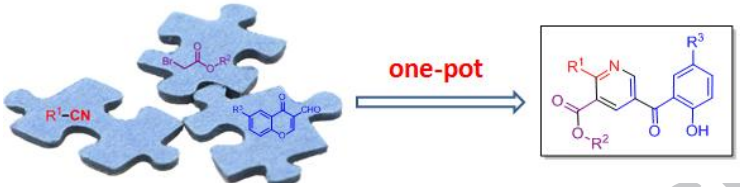

Highlights

1. A tandem synthesis of 2,3,5-substituted pyridine derivatives has been developed.
2. 3-cyanochromones have been used to extend the application.
3. Two similar mechanisms have been proposed, respectively.