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FULL PAPER

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Synthesis of benzofuro[2,3-c]pyridines via a one-pot three-component reaction

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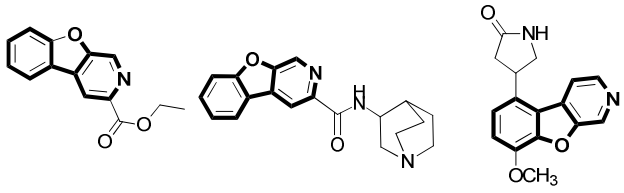
A convenient one-pot reaction was conducted by mixing bromoacetophenone, functional α, β-unsaturated ketone and potassium hydroxide in tetrahydrofuran at room temperature, ammonium acetate was added and heated to reflux, resulting in four chemical bonds from easily accessible substrates. This process provided a flexible and rapid synthetic route for the construction of polysubstituted benzofuro[2,3-c]pyridines in moderate to good yield.

Introduction

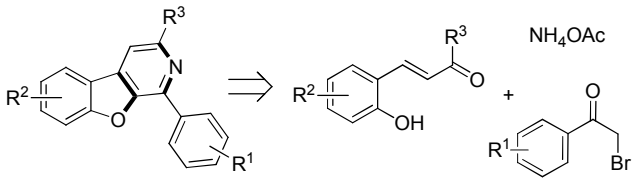
Heterocyclic compounds are abundant in nature. Benzofuropyridines represent an important class of heterocyclic compounds that exhibit a wide range of biological and pharmaceutical activities, including antitumor, antibacterial and antimalerial activities, and among others.[1] For example, research showed that ethyl benzofuro[2,3-c]pyridine-3-carboxylate（**I**） and its derivatives were able to be non-benzodiazepine structural ligands binding to benzodiazepine receptor in anxiolytics, tranquilizers, and anticonvulsants.[2] Benzofuro[2,3-c]pyridin-3-yl(quinuclidin-3-yl)methanone（**II**）had been reported for their central nervous system activity.[3] Benzofuro[2,3-c]pyridine and its derivatives （ **III** ） were useful as phosphodiesterase-10 inhibitors.[4] Because of these interesting biological activities, several synthetic routes have been developed to produce benzofuropyridines.[5] However, benzofuro[2,3-c]pyridines, considered as one of extremely significant benzofuropyridine structures, could be obtained through only few processes.[6-9] Srinivas and Marcel synthesized benzofuro[2,3-c]pyridines in 62% yield using functionalized alkynyl lithium and aryl magnesium reagents under -78 °C.[6] Lai and co-workers prepared benzofuro[2,3-c]pyridine in 63% yield using 3-fluoro-4-(2-methoxy-phenyl)-pyridine.[7] Furthermore, Wen reported the synthesis of benzofuro[2,3-c]pyridine utilizing α-and-γ activation of chloropyridines as well as palladium-mediated reactions.[8] Todd found that benzofurpyridines could be tolerated from oximes and alkynes via rhodium(III) catalysis in good yield.[9] However, the harsh reaction conditions (e.g. basic or anhydrous conditions) required by those processes limited their further applications, and there has not been a systematic pathway for the syntheses of such class of compounds. Therefore, it is urgent to develop an efficient and convenient method to construct benzofuro[2,3-c]pyridines.



I **II** **III**

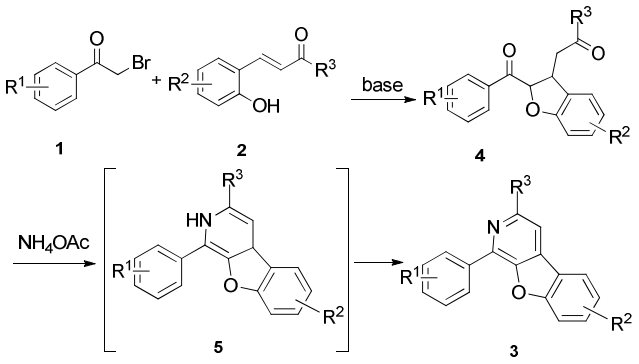
Multicomponent reaction (MCR) is becoming an attractive strategy for the facile construction of useful complex chemical compound and has been receiving considerable attention with the increasing economic and ecological pressure.[10] This novel approach provides diverse molecules in a one-pot reaction and proceeds in a highly efficient and atom-economical manner to generate multiple new bonds, which saves time and energy by avoiding multistep purifications of various intermediates.[11] Thus, developing a new MCR from simple and easily available substrates is one of the most important research topics in organic chemistry.

Our recent studies have been focusing on the development of new synthetic pathways for the preparation of cycle compounds, which was based on the use of cascade or one-pot reactions.[12] In this paper, using bromoacetophenones, 2-hydroxyphenyl functionalized α, β-unsaturated ketones and ammonium acetate (Scheme 1), we reported a one-pot three-component tandem procedure for the synthesis of benzofuro[2,3-c]pyridines under mild and metal-free conditions in good yield. To the best of our knowledge, this process was established for the first time for the tandem construction of the benzofuropyridines.



Scheme 1 Synthesis of benzofuropyridines via MCR.

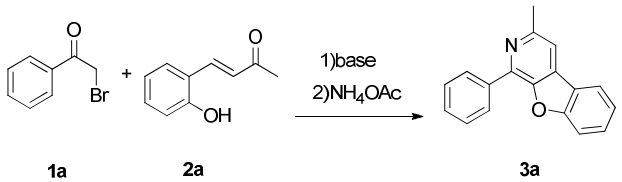
The first step of cascade reaction was critical, including a substitution reaction of halides **1** with 2-hydroxyphenyl functionalized α, β-unsaturated ketones **2**, and the formation of a new C-O bond.[13] Then, a C-C bond was produced through intramolecular michael addition reaction, yielding the intermediate product **4** that contained a 1, 5-dicarbonyl scaffold.[14] After the addition of ammonium acetate, pyridine ring systems were generated by formation of two bonds, from [5+1] atom fragments between 1, 5-dicarbonyl constructions and ammonium acetate.[15] The dihydropyridines **5** were formed first by dehydration reaction after ammonium acetate was added, and the processes of dehydrogenation oxidation were followed closely in air condition from dihydropyridines to pyridines without additional oxidants, The final products **3** were obtained as a pattern of benzofuro[2,3-c]pyridines. This new one-pot reaction provided an efficient method of synthetizing a complex fused pyridine system by simultaneous formation of four bonds from three readily accessible substrates.



Scheme 2 The proposed process for the tandem reaction.

To optimize the reaction conditions, we investigated the optimal conditions regarding both the base and the solvent. In particular, 2-bromoacetophenone **1a** (0.9 mmol), 4-(2-hydroxyphenyl)but-3-en-2-one **2a** (0.75 mmol) and ammonium acetate (4 mmol) were selected as a model reaction. Initially, organic bases such as DMAP and Et_3N and inorgarnic bases such as KOH, K_2CO_3, Na_2CO_3 and $NaHCO_3$ were investigated to the cascade reaction in THF. As summarized in Table 1 (entries 1-10), the choice of base significantly affected the yield. Most of bases could not promote this process efficiently, reactions with DMAP or Et_3N gave **3a** in less than 15% yield (entries 1-2) and a group of inorganic bases such as K_2CO_3, Na_2CO_3 and $NaHCO_3$ also yielded unsatisfied results (entries 3-5). KOH was found to be the most suitable base for the first step, with the yield of 74% (entry 6). Then the loading of KOH were also tested (entries 7-9), and 1.5 eq of KOH demonstrated the highest yield. Reaction was also performed in the presence of 6 mmol ammonium acetate, which had little influence on the yield of product (entry 10).

Table 1 Optimization of the reaction based conditions screening for the synthesis of benzofuro[2,3-c]pyridine[a]

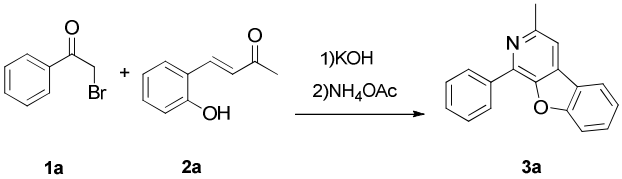


Entry	Based(eq.)	Solvent	Yield(%)[b]
1	DMAP(1.5 eq)	THF	11
2	Et_3N (1.5 eq)	THF	9
3	Na_2CO_3(1.5 eq)	THF	12
4	$NaHCO_3$(1.5 eq)	THF	trace
5	K_2CO_3(1.5 eq)	THF	25
6	**KOH(1.5 eq)**	**THF**	**74**
7	KOH(1.2 eq)	THF	26
8	KOH(1.4 eq)	THF	61
9	KOH(2.0 eq)	THF	55
10[c]	KOH(1.5 eq)	THF	73

[a]The first step of reactions were carried out using 2-bromoacetophenone (0.9 mmol), 4-(2-hydroxyphenyl)but-3-en-2-one (0.75 mmol) in the presence of catalyst in THF (15 mL) at room temperature. After the addition of ammonium acetate (4 mmol) and 5 mL C_2H_5OH, reactions were refluxed for 1 hour. [b]Yield of the isolated product after chromatography on silica gel. [c]6 mmol ammonium acetate was added to the reaction in THF.

In order to further improve the efficiency of this procedure, different solvents including toluene, dichloromethane, 1, 2-dichloroethane, methanol, ethanol, acetonitrile, tetrahydrofuran and water were used. The results displayed in Table 2, it indicated that no expected product was found when toluene was chosen as the reaction solvent (entry 1); On the other hand, dichloromethane and 1, 2-dichloroethane resulted in a poor yield around 10% (entries 2-3). A moderate yield could be obtained in alcohol and acetonitrile (entries 4-6). In order to further improve yield, we chose less solvent and lower temperature in this reaction, the results showed that the yield of the reaction increased to 77% in the presence of 5 mL THF, and the first-step reaction time also decreased to 30 min (entry 9). Longer reaction time in a lower temperature did not significantly improve the yield (entry 10), and the corresponding product was obtained in 75% yield. Yield declined rapidly with the addition of small amount of water while no products were gained in pure water (entries 7-8).

Table 2 Optimization of the reaction solvent conditions screening for the synthesis of benzofuro[2,3-c]pyridine[a]



Entry	Based(eq.)	Solvent	Yield(%)[b]
1	KOH(1.5 eq)	$PhCH_3$	trace
2	KOH1.5 eq)	CH_2Cl_2	9
3	KOH(1.5 eq)	$ClCH_2CH_2Cl$	11
4	KOH(1.5 eq)	C_2H_5OH	33
5	KOH(1.5 eq)	CH_3CN	52
6	KOH(1.5 eq)	CH_3OH	41
7	KOH1.5 eq)	H_2O	trace
8[c]	KOH(1.5 eq)	THF	31
9[d]	**KOH(1.5 eq)**	**THF**	**77**
10[e]	KOH(1.5 eq)	THF	75

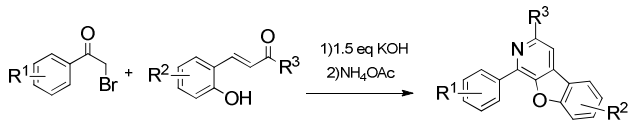
[a]The first step of reactions were carried out using 2-bromoacetophenone (0.9 mmol), 4-(2-hydroxyphenyl)but-3-en-2-one (0.75 mmol) in the presence of 1.5 eq KOH (1.125 mmol) with different solvent (15 mL) at room temperature. After the addition of ammonium acetate (4 mmol) and 5 mL C_2H_5OH, reactions were refluxed for 1 hour. [b]Yield of the isolated product after chromatography on silica gel. [c]The reaction was carried out in 12 mL THF and 3 mL H_2O. [d]The reaction was carried out in 5 mL THF. [e]The first step reaction was carried out at 0 °C for 6 hour.

We further probed the scope of two substrates for the cascade reaction under the optimal conditions, and it was found that all reactions of various bromoacetophenones, 2-hydroxyphenyl functionalized α, β-unsaturated ketones were suitable and led to corresponding benzofuro[2,3-c]pyridine derivatives in good yield (Table 3).

First, a scope of substrates on the bromoacetophenone were explored.[16] The results of various bromoacetophenones with 4-(2-hydroxyphenyl)but-3-en-2-one and ammonium acetate showed that the procedure could tolerate both aromatic bromoketones with electronically different substituents, and it was observed that the substituents on the aromatic rings had some influences on the yields of the products. No matter whether bromoacetophenone with electron-withdrawing groups (Table 3, entries 2-3), or electron-donating groups, such as methyl, methoxyl and tert-butyl groups (Table 3, entries 4-8) on aromatic rings were used, the reactions proceeded to give slightly lower yields. And electron-donating substrates gave superior yields (55%-74%) while electron-withdrawing substrates only took place in 42%-46% isolated yields.

Then, a scope of substitutional 2-hydroxyphenyl functionalized α, β-unsaturated ketones with methyl group on the carbonyl[17] were extended and the similar reactivity was observed. In most cases, adducts were obtained in moderate yields (Table 3, entries 9-14). 5-tert-butyl group and 3,5-di-tert-butyl group on the aromatic rings worked better in the process and resulted in 71% and 78% yields (Table 3, entries 11 and 12), respectively. However, substrates with other electron-donating groups, such as methyl group afforded lower yields (Table 3, entries 13-14). The cascade reactions not only worked out with alkyl 2-hydroxyphenyl functionalized α, β-unsaturated ketones, but also with less reactive aromatic systems at both ends with high yields[18] (Table 3, entries 15-21). It was interesting to find that functionalized α, β-unsaturated ketones with aromatic group on the carbonyl could consistently produce moderate to excellent yields in the reactions. It was worthy of noting that either substrates with electron-withdrawing (Table 3, entries 16-19) or electron-donating (Table 3, entries 20-21) groups on aromatic rings could offer higher yields than electron-neutral group (entry 15), and a higher yield would occur when aromatic group with meta substituent on the carbonyl compared with para-, ortho-substituted aromatic ring (Table 3, entries 16-19). The best result was obtained in 83% yield (Table 3, entry 21) when functionalized α, β-unsaturated ketone substrate with 4-CH_3-Ph group on the carbonyl was investigated.

Table 3 The cascade reaction of various substrates for the synthesis of benzofuro[2,3-c]pyridine derivatives[a]



1 2 3

Entry	R^1	R^2	R^3	Yield[b] (%)
1	H	H	CH_3	77**(3a)**
2	3-Br	H	CH_3	46**(3b)**
3	4-Br	H	CH_3	42**(3c)**
4	4-OCH_3	H	CH_3	55**(3d)**
5	2-CH_3	H	CH_3	74**(3e)**
6	3-CH_3	H	CH_3	59**(3f)**
7	4-CH_3	H	CH_3	68**(3g)**
8	4-tert-butyl	H	CH_3	71**(3h)**
9	H	5-Cl	CH_3	46**(3i)**
10	H	5-Br	CH_3	44**(3j)**
11	H	5- tert-butyl	CH_3	71**(3k)**
12	H	3.5-di-tert-butyl	CH_3	78**(3l)**
13	H	3.5-di-methyl	CH_3	57**(3m)**
14	H	4.5-di-methyl	CH_3	63**(3n)**
15	H	H	Ph	32**(3o)**
16	H	H	4-Br-Ph	75**(3p)**
17	H	H	3-Br-Ph	81**(3q)**
18	H	H	2-Cl-Ph	55**(3r)**
19	H	H	4-Cl-Ph	63**(3s)**
20	H	H	4-CH_3O-Ph	65**(3t)**
21	H	H	4-CH_3-Ph	83**(3u)**

[a]Reaction condition: The first step of reactions, bromoacetophenone derivatives (0.9 mmol), 2-hydroxyphenyl functionalized α, β-unsaturated ketone derivatives (0.75 mmol), 1.5 eq KOH (1.125 mmol) in 5 mL THF at room temperature, after the addition of ammonium acetate (4 mmol) and 5 mL C_2H_5OH, reactions were refluxed. [b]Yield of the isolated product after chromatography on silica gel.

To get a preliminary understanding of the reaction mechanism, we tried to identify the intermediates in the reaction. As 1, 5-dicarbonyl construction was proposed as an intermediate **4a**, we traped it by mixing 2-bromoacetophenone **1a**, 4-(2-hydroxyphenyl)but-3-en-2-one **2a** and potassium hydroxide in tetrahydrofuran at room temperature. It was observed in 95% yield after purified by column chromatography, and NMR was carried out to confirm the intermediate **4a** structure.

The following experiments were then conducted to confirm that 1-(2-benzoyl-2,3-dihydrobenzofuran-3-yl)propan-2-one **4a** could be converted into the final product under the standard conditions : When intermediate **4a** was applied under the reaction conditions with 10 equivalent of ammonium acetate in 5 mL C_2H_5OH, 69% of the desired product **3a** was obtained, which confirmed that **4a** was indeed an intermediate.

Conclusions

In conclusion, we have developed a one-pot procedure for the synthesis of polysubstituted benzofuro[2,3-c]pyridines in good yield. The sequence reaction contained a convenient substitution–Michael addition cascade reaction that formed a 1, 5-dicarbonyl scaffold from easily accessible bromoacetophenone and 2-hydroxyphenyl functionalized α, β-unsaturated ketones, followed

by a dehydration-cyclization and dehydrogenation procedures with the addition of ammonium acetate. This method not only offers tangible improvements in the reaction rates and yields under mild and metal-free conditions, but also avoids the use of hazardous catalysts and reagents. Moreover, the cascade reaction has been successfully applied in a scope of substituents on the bromoacetophenones and functionalized α, β-unsaturated ketones with methyl or aromatic group on the carbonyl. The broad scope of this one-pot reaction makes this procedure promising for practical usages. For future works, investigation of the application and the design of new synthetic craft for these products are ongoing in our laboratory.

Experimental

Materials

Commercially available solvents were used as received. Some bromoacetophenone compounds were prepared accoording to the reported method, other chemicals were purchased from Aladdin.

General experimental procedures

Synthesis of substituted benzofuro[2,3-c]pyridines 3a-u. Compound **1** (0.9 mmol) and compound **2** (0.75 mmol) was dissolved in THF (5 mL), KOH (1.125 mmol) was slowly added and the mixture was stirred at room temperature until the reaction was completed (monitored by TLC). Ammonium acetate (4 mmol) and 5 mL C_2H_5OH were added to the reaction mixture and heated to reflux. The reaction mixture was cooled to room temperature, solvent was removed under reduced pressure and the residue was purified by column chromatography to afford the desired products **3**.

Synthesis of substituted 1-(2-benzoyl-2,3-dihydrobenzofuran-3-yl)propan-2-one 4a. Compound **1a** (179 mg, 0.9 mmol) and compound **2a** (122 mg, 0.75 mmol) was dissolved in dry THF (5 mL), KOH (63 mg, 1.125 mmol) was slowly added and the mixture was stirred at room temperature until the reaction was completed (monitored by TLC). The reaction mixture was then adsorbed onto silica gel, loaded on a silica column, and eluted with a mixture of ethyl acetate in petroleum ether. The compounds obtained after column chromatography are generally pale yellow solid **4a** 200mg in 95% yield.

Acknowledgment

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