Novel Synthesis of Pyrido[2,1-*a*]isoindoles via a Three-Component Assembly Involving Benzynes

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Received 12 July 2008

Abstract: A novel three-component assembly involving benzynes has been developed for the synthesis of pyrido[2,1-*a*]isoindoles in moderate yields. Reaction conditions have been optimized and the scope of the reaction has been studied. A plausible mechanism has been proposed to account for the three-component reaction.

Key words: three component, benzyne, aryne, pyrido[2,1-*a*]isoindole

Pyrido[2,1-*a*]isoindoles are important core structures of many pharmaceuticals[1] and functional materials.[2] In spite of the wide applications, the synthetic methods of this framework are quite scarce. The most frequently used method to construct these motifs is the free radical cyclization strategies.[3] However, these methods generally require strict reaction conditions and involve multistep reactions.

Multicomponent reactions have attracted a lot of attention in recent years [4] due to their rapid elaboration of complex structure in a highly efficient and modular manner, and the formation of several bonds in one single step is highly compatible with the goals of 'green chemistry' and atom economy. The application of this strategy in the syntheses of heterocycles has become an attractive field in recent years[5–7] in light of the paramount role of these targets in the natural products, pharmaceuticals and functional materials.

Arynes are one of the most important organic species and have been frequently used as intermediates in a variety of reactions.[8] Recently, multicomponent reactions involving arynes have attracted much attention.[9] For example, Yamamoto and his co-workers have reported the palladium-catalyzed co-cyclizations of arynes, alkenes and alkynes.[10] Moreover, Wang and his co-workers have developed a three-component cascade reaction involving arynes, aldehydes and amines.[11] During our continuous explorations on new reactions involving arynes,[12] we found that a kind of betaine structure like **1B** (Scheme 1) can be accessed in a single step via a three-component reaction of benzynes, pyridines, and α-halogenated ketones.

We initiated our experiments by using benzyne, which was generated in situ from the elimination of *o*-trimethylsilyl phenyltriflate induced by CsF, reacting with 2-bromo-1-phenylethanone and pyridine in MeCN at 80 °C for 24 hours. Several products were observed and the main product was easily isolated by silica gel column chromatography. After the characterization of the main product by ^{1}H NMR, ^{13}C NMR and HRMS, the exact structure was still ambiguous. We finally identified the exact structure by the X-ray diffraction analysis of the single crystal of the product (Figure 1 and see the supplementary information).[13] It appears that the resonance structure **1B** contributed more to the NMR data of the product (Scheme 1), which led to the chemical shifts of proton on carbon next to nitrogen emerging in very low-field range.

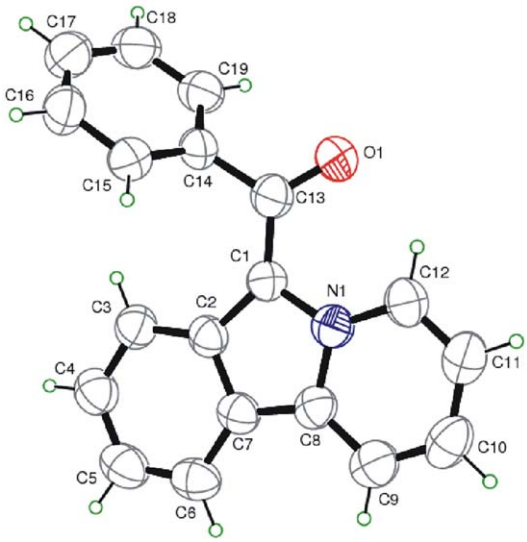
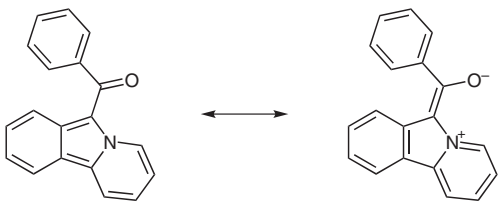


Figure 1 Representation of the X-ray crystal structure of product **1**



1A **1B**

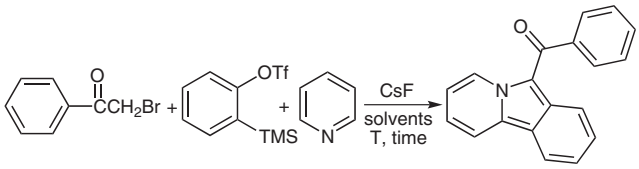
Scheme 1 The resonance of **1A** and **1B**

SYNLETT 2008, No. 20, pp 3115–3120
Advanced online publication: 27.11.2008
DOI: 10.1055/s-0028-1087417; Art ID: W11108ST

We next optimized the reaction conditions of this three-component assembly and the results are summarized in Table 1. Solvents frequently used in aryne chemistry such as toluene, THF, DME and MeCN were employed as the reaction media at their respective refluxing temperatures, and the best result was obtained when MeCN was used (Table 1, entries 1–4). Lowering the reaction temperature from 80 °C to room temperature led to the decrease in the yields (Table 1, entries 5–7). When the reaction was carried out in refluxing MeCN for two hours, a comparable yield was obtained to that for 24 hours (Table 1, entry 8). Further shortening of the reaction time led to lower yields (Table 1, entries 9 and 10). The best result was obtained when the reaction was conducted in refluxing MeCN for two hours, leading to a 56% yield of pyrido[2,1-*a*]isoindole product.

With the optimized reaction conditions in hand, we turned to investigate the scope of the three-component reaction and some typical results are summarized in Table 2. Under the standard reaction conditions, various substituted 2-bromo-1-phenylethanones underwent the reaction smoothly, while 2-bromo-1-phenylethanones bearing electron-donating groups gave better yields than those bearing electron-withdrawing groups (Table 2, entries 3, 5, 7 and 9). It had to be noted that benzyne with two symmetric methyl groups could also take part in the three-component reaction efficiently and afforded products in moderate yields (Table 2, entries 2, 4, 6, 8 and 10). Moreover, good results were also obtained when substituted pyridine like 4-picoline underwent the reaction (Table 2, entries 11 and 12). Other nitrogen-containing heterocycle such as isoquinoline could also react with 2-bromo-1-phenylethanone and benzynes to afford the corresponding products efficiently (Table 2, entries 13 and 14).

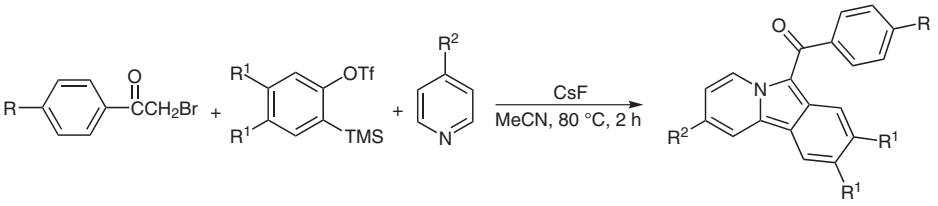
Table 1 The Optimization Studies[a]



Entry	Solvent	T (°C)[b]	Time (h)	Yield (%)[c]
1	Toluene	110	24	Trace
2	THF	67	24	8
3	DME	80	24	39
4	MeCN	80	24	57
5	MeCN	60	24	50
6	MeCN	40	24	40
7	MeCN	25	24	36
8	MeCN	80	2	56
9	MeCN	80	1	52
10	MeCN	80	0.5	38

[a] Reaction conditions: 2-bromo-1-phenylethanone (0.6 mmol), pyridine (1.0 mmol), benzyne precursor (0.5 mmol), CsF (1.5 mmol), solvents (5.0 mL).
[b] Bath temperature.
[c] Isolated yields.

Table 2 Scope of the Reaction[a]



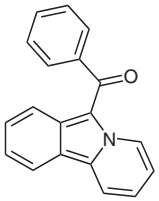
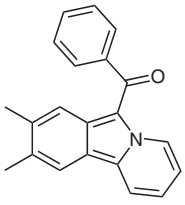
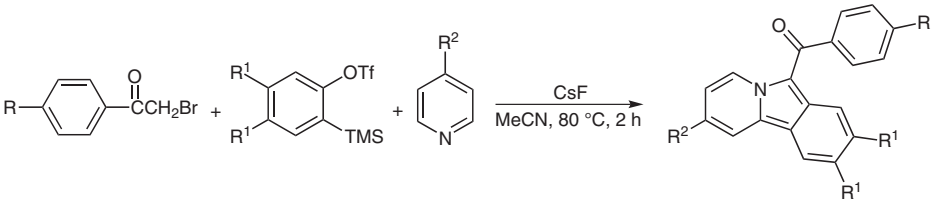
Entry	R	R^1	R^2	Product	Yield (%)[b]
1	H	H	H		56
2	H	Me	H		47

Table 2 Scope of the Reaction[a] (continued)



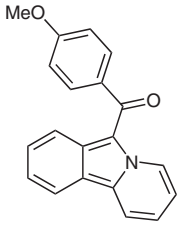
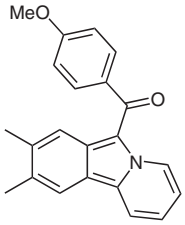
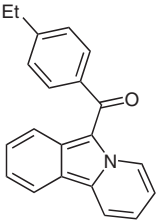
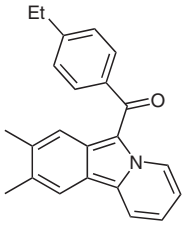
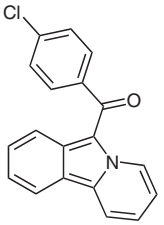
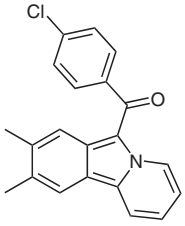
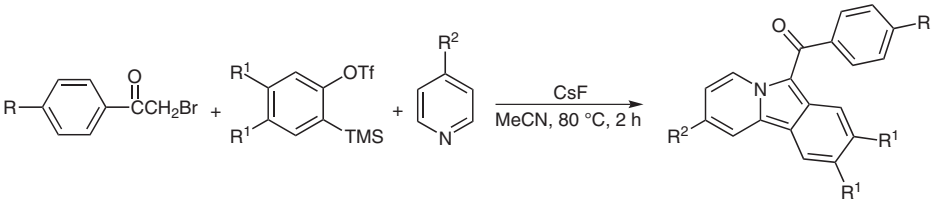
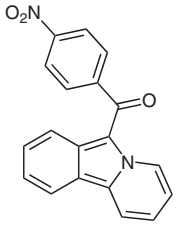
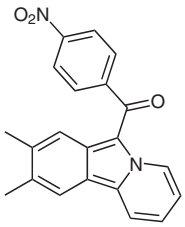
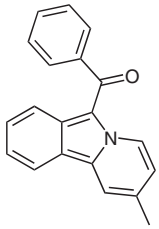
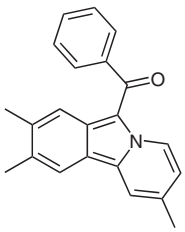
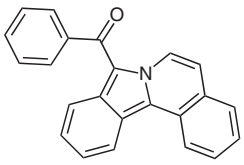
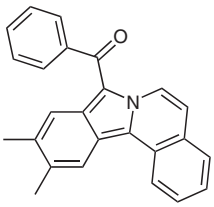
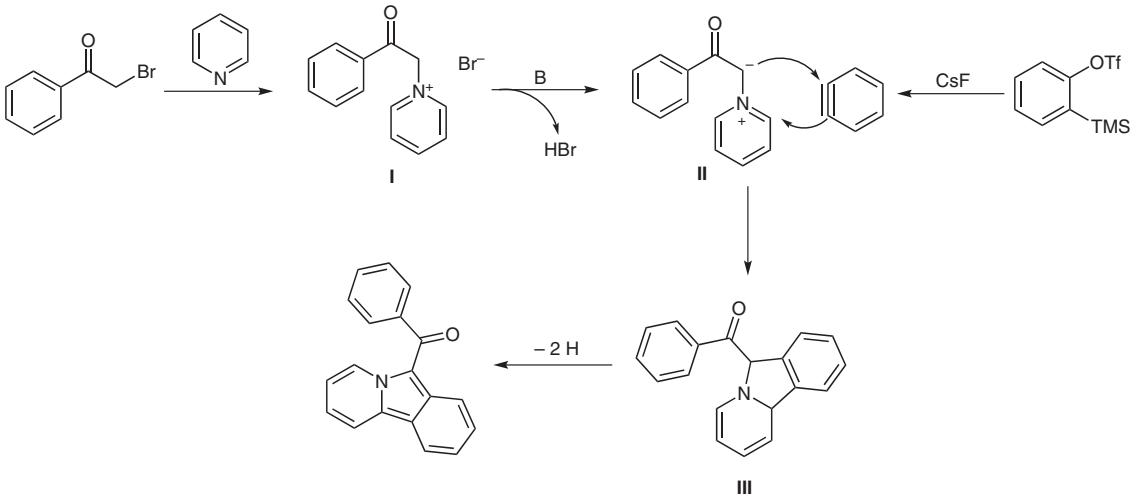
Entry	R	R^1	R^2	Product	Yield (%)[b]
3	MeO	H	H		60
4	MeO	Me	H		47
5	Et	H	H		57
6	Et	Me	H		45
7	Cl	H	H		41
8	Cl	Me	H		35

Table 2 Scope of the Reaction[a] (continued)



Entry	R	R^1	R^2	Product	Yield (%)[b]
9	NO_2	H	H		36
10	NO_2	Me	H		31
11	H	H	4-Me		56
12	H	Me	4-Me		53
13	H	H	isoquinoline		51
14	H	Me	isoquinoline		45

[a] Reaction conditions: 2-bromo-1-phenylethanones (0.6 mmol), pyridines (1.0 mmol), benzyne precursors (0.5 mmol), CsF (1.5 mmol), MeCN (5.0 mL), 80 °C (bath temperature), 2 h.
[b] Isolated yields.



Scheme 2 Proposed mechanism

Based on the above results, a plausible reaction mechanism is proposed (Scheme 2). The initial step involved the generation of a cationic species **I** from the reaction of 2-bromo-1-phenylethanone with pyridine, which then eliminated one molecular HBr to form the 1,3-diplor intermediate **II**. The subsequent cycloaddition between the intermediate **II** and benzyne species, which was generated in situ from the fluoride induced 1,2-elimination of *o*-trimethylsilyl phenyltriflate, produced the annulation product **III**. A dehydrogenated aromatization of **III** then liberated the final pyrido[2,1-*a*]isoindole product.

In conclusion, a novel three-component assembly involving benzynes, which can be used for the syntheses of pyrido[2,1-*a*]isoindole structure, has been developed in our laboratory.[14,15] The exact structure of the product has been identified by the X-ray crystallographic analysis. The reaction conditions have been optimized and the scope of the reaction has been investigated. Further mechanism exploration and application studies of the products are currently ongoing in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We thank the support of the Zhejiang Provincial Natural Science Foundation of China (R407106) and the Natural Science Foundation of China (No. 20571063).

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(13) The CCDC number of the X-ray structure is 701719.
(14) (a) All the reactions were carried out under the nitrogen atmosphere in oven-dried flasks. MeCN was distilled from CaH_2 using benzophenone as the indicator. 2-Bromo-1-(4-methoxyphenyl)ethanone, 2-bromo-1-(4-ethylphenyl)-ethanone, 2-bromo-1-(4-nitrophenyl)ethanone, 2-bromo-1-(4-chlorophenyl)ethanone were prepared according to the method described in: Ismail, M. A.; Brun, R.; Wenzler, T.; Tanious, F. A.; Wilson, W. D.; Boykin, D. W. *J. Med. Chem.* **2004**, *47*, 3658. (b) Benzyne precursors were prepared according to the method of: Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, *12*, 1211. (c) Other materials were purchased from common commercial sources and used without additional purification. ^{1}H NMR spectra were recorded at 400 MHz using TMS as internal standard. ^{13}C NMR spectra were recorded at 100 MHz using TMS as internal standard. Mass spectroscopy data of the reaction product were collected on an HRMS (EI) instrument.
(15) **General Procedure of the Three-Component Reaction**: An oven-dried flask was charged with 2-bromo-1-phenyl-ethanone (0.6 mmol), pyridine (1.0 mmol), CsF (1.5 mmol) and MeCN (3 mL). Benzyne precursor (0.5 mmol) in MeCN (2 mL) was added dropwise under the protection of N_2. The reaction mixture was then allowed to react at 80 °C for 2 h. After the completion of the reaction, the mixture was cooled to r.t. and filtered through a pad of celite. The solvent was then removed in vacuum, and the final product was obtained by flash chromatography on a silica gel column as a yellow powder.