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Potassium *tert*-butoxide-mediated generation of arynes from *o*-bromoacetophenone derivatives

Denghu Chang [1], Fei Gao [1], Lei Shi [*]

Shenzhen Graduate School, Harbin Institute of Technology, Shenzhen 518055, China

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o-bromoacetophenone derivatives as new versatile aryne precursors are induced to selectively eliminate the C_{Ar}—Br and C_{Ar}—$C_{(Ac)}$ bonds in the help of *t*-BuOK. Furthermore, the active aryne intermediates are successfully applied in a substantial set of reactions including *N*-arylation and copper-catalyzed coupling with various terminal alkynes. It is important to note that the generation of benzyne intermediate is demonstrated through cycloadditon reaction experiment with furan.

1. Introduction

Arynes have been recognized as useful reactive intermediates in synthetic organic chemistry due to the presence of a highly distorted triple bond in the six-membered carbacycle.[1] Numerous reactions, employing aryne species which are generated *in situ* from various precursors, have been developed.[2] The formal *ortho*-elimination reactions in which a precursor arene loses one or more groups are the most main strategies. Remarkably, in recent years the introduction of *ortho*-silylaryl triflates as benzyne precursors[3] has been supposed an important advance in this field. Typically, the simple treatment of these reagents with fluoride allows the easy generation of arynes to be applied in manifold types of reactions under mild conditions, such as arylations, insertion reactions, cycloaddition reactions and multicomponent reactions (MCR).[4]

Despite the significant advances, however, there are still some drawbacks associated with these approaches: (1) the syntheses of these precursors need 3–5 steps; (2) the instability of triflates; (3) the high cost of triflating reagents and (4) the formation of potentially genotoxic trifluoromethanesulfonate side product. Notably, since Roberts firstly reported arynes *via* chlorobenzene with KNH_2 in 1953,[5] the interest in aryne chemistry has grown in parallel with fluoride-free strategies in which a number of precursors to arynes and their activators involving diazonium carboxylates,[6] iodonium triflates,[7] benzotriazole,[8] aryl halides[9] and *ortho*-borylaryl triflates[10] were reported. For instance, benzynes, generated under Knochel conditions through I—Mg exchange of 2-iodophenylsulfonates and *i*PrMgCl, smoothly were added by thiol, selenol, and amine nucleophiles with functional groups like ester, nitrile, and nitro which prove, in some cases, to be orthogonal to those of 2-trimethylsilylaryl triflates.[11] Pd-mediated generation of benzyne *via* a decarboxylation from the cheap 2-bromobenzoates[12] or benzoic acids[13] was also reported, and then underwent [2 + 2+2] trimerisation to afford triphenylenes. To sum up, establishing a general method for aryne generation to overcome the certain issues associated with *ortho*-silylaryl triflates still remains a salient challenge.

In recent years, transition-metal-free version of reaction process has gained immense interest in green and sustainable chemistry synthesis.[14] In 2008, Itami first revealed the *t*-BuOK promoted C—H bond arylation of heterocycles by using haloarenes under microwave irradiation.[15] Subsequently, Hayashi,[16a] Lei[16b] and Shi[16c] independently developed this methodology on base-promoted homolytic aromatic substitution (HAS) of unactivated arenes.[17] Since then, considerable efforts have been made towards the explorement of other coupling reactions, such as intramolecular cyclization, Heck-type coupling, carbonylation under *t*-butoxides (eg. *t*-BuOK) mediated conditions.[18]

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[*] Corresponding author.
E-mail address: lshi@hit.edu.cn (L. Shi).
[1] These authors contributed equally.

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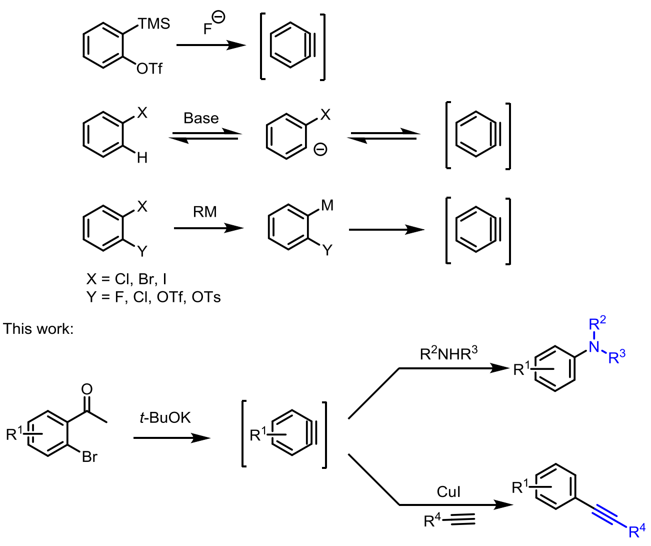
Inspired by the *t*-BuOK promoted cross-coupling methodology,[19] herein we developed a useful method for the synthesis of aryne intermediate generated *in situ* from commercially available *o*-bromoacetophenone derivatives *via* the readily elimination of *o*-bromoacylates (Scheme 1). Aryl amines and alkynes are extremely important building blocks because of their potential applications in pharmaceuticals, organic materials and natural products.[20] Larock[21] and Zhang[22] have disclosed the *N*-arylation of amines and copper-catalyzed two-component coupling reaction of terminal alkynes with arynes formed by *ortho*-silylaryl triflates. Following this study, to our delight, cheap *o*-bromoacetophenone derivatives, as new aryne precursors, were successfully applied in the *N*-arylation and copper-catalyzed coupling reaction systems to obtain the corresponding arylated products in moderate to good yields. Importantly, compared with the prosperous achievements, our strategy avoided the formation of potentially genotoxic byproduct.

2. Results and discussion

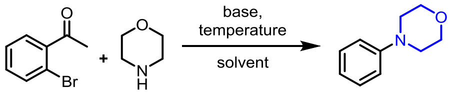
Our optimization studies of this process are summarized in Table 1. The use of CsF, and Cs_2CO_3, failed to provide the desired product under analogous conditions (entries 1 and 2). The use of KOH or $NaNH_2$, a stronger base, also did not lead to formation of the desired 4-phenylmorpholine (entries 3 and 4). To our delight, when K_2CO_3 was used, the corresponding product (**2a**) was observed (entry 5). Importantly, the key modification to achieve a higher yield was the use of *t*-BuOK, which significantly affected both the rate and outcome, and yielded up to 87% after flash column chromatography purification. In addition, a variety of solvents were screened although dioxane appeared the most suitable of those examined (entries 7 and 8). At lower temperature (110 °C) the reaction leaded to a lower yield of 70% (entry 9). *n*-BuLi was also examined, however, a dramatically decreased yield was observed. Based on the facts mentioned above, the reaction conditions described in entry 6 were selected as the standard condition for further investigations of facile *N*-arylation of amines.

Under the standard reaction conditions, a variety of substituted amines were studied in Table 2. As might be anticipated, sencondary alkylamines (**2a**-**e**) reacted well with the aryne precursor to afford *N*-arylated alkylamines (**3a**-**e**) in good yields (74–87%). The mono-*N*-arylation of primary amine was obtained in a moderate yield (**3f**, 48%), probably due to the subsequent diarylation. On the other hand, indole has also proven to be a good substrate for *N*-arylation (**3g**, 66%). Next, the arylation of sterically hindered *N*,*N*-dibenzylaniline was accomplished in a fair yield (**3h**, 46%). It should be pointed out that a variety of other benzyne precursors including methyl and methoxy groups, were investigated under our reaction conditions. When methyl-substituted *o*-bromoacetophnone was employed with morpholine, two isomers were obtained in almost equal amounts (**3i**, 72%). In addition, the methoxy-substituted *o*-bromoacetophnone reacted cleanly to generate a single regioisomer arylation product (**3j**, 80%), which was rationalized by the corresponding symmetrical benzyne intermediate formed in the process.



Scheme 1. Methods of aryne generation.

Table 1
Optimization of reaction conditions[a].



1a **2a** **3a**

Entry	Base	Temperature	Solvent	Yield (%)[b]
1	CsF	140 °C	dioxane	0
2	Cs_2CO_3	140 °C	dioxane	0
3	KOH	140 °C	dioxane	0
4	$NaNH_2$	140 °C	dioxane	0
5	K_2CO_3	140 °C	dioxane	9
6	*t*-BuOK	140 °C	dioxane	87
7	*t*-BuOK	140 °C	DMSO	52
8	*t*-BuOK	140 °C	DMF	trace
9	*t*-BuOK	110 °C	dioxane	70
10	*n*-BuLi	140 °C	THF	11
11	*n*-BuLi	140 °C	dioxane	9
12[c]	*t*-BuOK	140 °C	dioxane	0

[a] Reaction conditions: 1-(2-bromophenyl)ethan-1-one (1.0 mmol), morpholine (2.0 equiv), base (2.0 equiv), solvent (5 mL), 16 h, under N_2, without light.

[b] Isolated yield based on **1a**.

[c] 10% $Pd(OAc)_2$ was added.

To evaluate the potential of our system, we turned our attention to explore two substituents on the aryl groups with various benzyne precursors as illustrated in Table 3. Notably, when the substrates incorporated with propionyl, isobutyryl or 2-phenylacetyl instead of acetyl were employed, the reaction worked smoothly to deliver the desired product **3a** (Table 3, entries 1–3). This revealed that the reaction might start through an acidic α-hydrogen abstraction. Furthermore, changing halide Br to the *O*-tosylated, trifluoromethanesulfonyl or mesyl esters, the *N*-arylation was fully suppressed under the general reaction conditions, which probably retarded the *o*-elimination process (Table 3, entries 4–6). To our delight, changing Br to other halide such as Cl or I, the expected product was successfully obtained with a good isolated yield, and it showed the halides had major influence on the reaction (Table 3, entries 7–8).

During further studies, we performed the coupling of aryne generated *in situ* from *o*-bromoacetophnone and phenyl acetylene in the present of copper catalyst (Table 4). Gratifyingly, the desired dipehenyl acetylene **5a** was isolated in 74% yield without any ligands. As expected, various aryl substituents (Me, F) in aryl alkynes were well tolerated under the reaction conditions and the desired coupling products were obtained in 67% and 58%, respectively (**5b** and **5c**). Besides, the aliphatic terminal alkyne could also be converted into the corresponding product **5d**, albeit in 23% yield, owing to the low boiling point of pent-1-yne **4d**. It should be noted that 4-methyl-substituted aryne readily participated in the reaction (**5e**, 67%) and led to two regioisomers in a ratio of 1:1, indicating that it