

# Communication

# Selective arylation/annulation cascade reactions of 2-alkynylanilines with diaryliodonium salts



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### ARTICLE INFO

Article history: Received 16 July 2016 Accepted 13 September 2016 Published 5 November 2016

Keywords: Selective arylation Annulation Diaryliodonium salt 2-Alkynylaniline N-Aryl indole Cascade reaction ABSTRACT

An efficient Cu catalyzed selective arylation/annulation cascade reaction of 2-alkynylanilines with diaryliodonium salts was developed. This reaction was selective to *N*-arylation instead of *C*-arylation, which provides a simple synthetic method for *N*-aryl indoles.

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Diaryliodonium salts are used in versatile organic transformations because of their highly electron-deficient nature and excellent leaving-group ability [1]. As mild, nontoxic, and selective reagents, they are competent arylating agents in organic synthesis [2,3], especially in constructing C–C [4–13] and C–X [14–17] bonds. Among these, nucleophilic substitution reactions between diaryliodonium salts with nitrogen nucleophiles have received much attention [18–21]. Recently, Guant's group [7] reported aromatic electrophile equivalents generated from the combination of diaryliodonium salts and copper catalysts via the intermediacy of Cu(III)–aryl species. These active species were considered to be responsible for the high activity of the diaryliodonium salts in Cu catalyzed reactions.

Indoles are one of the most ubiquitous heterocycles found in nature. Owing to their significant biological activity, indoles are central structural motifs in making numerous pharmacologically important compounds [22]. Consequently, much attention has been paid to their preparation, which is a major research area in organic synthesis and many methods have been developed [23]. Meanwhile, the cyclization of 2-alkynylaniline derivatives has long been exploited for the construction of indoles [24,25].

Although diaryliodonium salts have been applied to a number of arylation reactions with substrates possessing single nucleophilic group, the selective arylation of the substrates with two or more nucleophilic groups is still a challenging subject [4,6]. For example, it was disclosed that although *C*-arylation and *N*-arylation can be achieved by diaryliodonium salts, the selectivity is still a challenge. The key to solving this is how to exploit the difference in the nucleophilic groups. Here, we reported an example of a selective *N*-arylation reaction of 2-alkynylanilines with diaryliodonium salts where subse-

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This work was supported by the Intercollegiate Key Scientific Research Projects of Henan Province (15A150018).

DOI: 10.1016/S1872-2067(16)62522-6 | http://www.sciencedirect.com/science/journal/18722067 | Chin. J. Catal., Vol. 37, No. 11, November 2016



**Scheme 1.** Reaction of 2-alkynylaniline (**1a**) and diphenyliodonium salt (**2a**).

quently the untouched *C*-nucleophile behaved as another reactive site to complete arylation-annulation cascade reactions to afford *N*-aryl indoles [26–28] (Scheme 1).

We first examined the reaction of 2-(phenylethynyl)aniline (1a) and diphenyliodonium triflate (2a). First, to overcome the possible competition of N-arylindoles and C-arylation, 1,2-dichloroethane (DCE) was placed on the top of the solvent list because it has been demonstrated to favor N-aryltaion [4]. No reaction occurred when the metal catalyst was omitted. A Cu catalyst system has been shown to be effective in both the arylation and annulation of 2-alkynylanilines [29]. Both copper(I) and copper(II) salts were effective for this reaction, and the use of 10 mol% Cu(OCOC<sub>8</sub>H<sub>17</sub>)<sub>2</sub> (copper 2-ethylhexoate) gave the desired product 3a in 93% yield. Meanwhile, the use of CuCl, CuBr, CuI, CuSCN and Cu(OTf)2 resulted in decreased yields (Table 1, entries 1-8). Then the screening of the base exhibited that N,N-diisopropylethylamine (DIPEA) was more effective than the other bases (Et<sub>3</sub>N, K<sub>2</sub>CO<sub>3</sub>, KOtBu and K<sub>3</sub>PO<sub>4</sub>, Table 1, entries 9-12). The influence of the solvent on the reac-

#### Table 1

Optimization of the reaction conditions.

	+ $(Ph)_2IOTf$	[Cu], base Solvent, reflu	<b>*</b>	Ph	
1a NH <sub>2</sub>	2a		3a Ph		
Entry	[Cu]	Base	Solvent	Yield <sup>a</sup> (%)	
1	—	DIPEA	DCE	<5	
2	CuCl	DIPEA	DCE	56	
3	CuBr	DIPEA	DCE	61	
4	CuI	DIPEA	DCE	67	
5	CuSCN	DIPEA	DCE	67	
6	CuBF4(MeCN)4	DIPEA	DCE	80	
7	Cu(OTf)2	DIPEA	DCE	61	
8	$Cu(OCOC_8H_{17})_2$	DIPEA	DCE	93	
9	$Cu(OCOC_8H_{17})_2$	Et <sub>3</sub> N	DCE	69	
10	$Cu(OCOC_8H_{17})_2$	K <sub>2</sub> CO <sub>3</sub>	DCE	<5	
11	$Cu(OCOC_8H_{17})_2$	KO <sup>t</sup> Bu	DCE	26	
12	$Cu(OCOC_8H_{17})_2$	K <sub>3</sub> PO <sub>4</sub>	DCE	<5	
13	$Cu(OCOC_8H_{17})_2$	DIPEA	Toluene	69	
14	$Cu(OCOC_8H_{17})_2$	DIPEA	$CH_2Cl_2$	56	
15	$Cu(OCOC_8H_{17})_2$	DIPEA	CHCl <sub>3</sub>	35	
16	$Cu(OCOC_8H_{17})_2$	DIPEA	THF	20	
17 <sup>b</sup>	$Cu(OCOC_8H_{17})_2$	DIPEA	DCE	22	
18 c	$Cu(OCOC_8H_{17})_2$	DIPEA	DCE	48	
19 <sup>d</sup>	$Cu(OCOC_8H_{17})_2$	DIPEA	DCE	43	

Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), [Cu] (10 mol%), base (0.4 mmol), solvent (2.0 mL), 1 h. <sup>a</sup> Isolated yields. <sup>b</sup> Diphenyliodonium chloride used. <sup>c</sup> Diphenyliodonium hexafluorophosphate used. <sup>d</sup> Diphenyliodonium tetrafluoroborate used.

tion was also examined. The result showed that DCE was the best choice while a decreased yield of the desired product was observed in solvents such as toluene, CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub> and THF (Table 1, entries 13–16). The counter-ions of the diphenyliodonium salt were also evaluated. The result showed that diphenyliodonium traflate was superior to diphenyliodonium chloride, diphenyliodonium hexafluorophosphate and diphenyliodonium tetrafluoroborate (Table 1, entries 17–19).

With these optimized reaction conditions in hand, we next elucidated the substrate scope of the cascade reaction. First, various o-alkynylanilines 1 with diphenyliodonium triflate (2a) were employed in the reaction. The results are compiled in Scheme 2. Generally, the reactions proceeded smoothly to afford the corresponding indoles 3 in isolated yields of 79%–97%. The reaction went well when  $R^1$  = aryl group while the electronic nature of the substituent on the benzene ring of  $\mathbb{R}^1$ was varied. Both electron-withdrawing and electron-donating groups were tolerated. Notably, it was found that alkynes bearing alkenyl (R1 = alkenyl group) or alkyl groups (R1 = alkyl group) on the alkyne terminus were also compatible, providing the products 3e-3g in good to excellent yields of 79%-92%. Substitution with 4-Me or 4-Cl functionalities on the parent aryl ring also afforded **3h** and **3i** in high yields of 89% and 97%, respectively.

The scope of the reaction was also investigated by varying the diaryliodonium triflate. The results are summarized in Scheme 3. Interestingly, the sterically demanding di(*o*-methylpheny)liodonium triflate **2b** gave product **4b** in good yield (82%). Higher yields (**4c**-**4f**) were obtained with less sterically demanding diaryliodonium triflates. Also, the substituent nature of R<sup>1</sup> has some influence on the reaction (**4f** vs **4g**). Substrates with substituent on the benzene ring (**1h**) reacted with diaryliodonium triflate to afford **4h** with good to excellent yields (82% and 98%, respectively).

The reaction of **1a** and unsymmetric diaryliodonium salt **2i** was also evaluated. Aryl with a lesser steric effect could be transferred to **1a**, and **4i** was obtained in 80% yield (Scheme 4).



Scheme 2. Synthesis of *N*-phenyl indoles (3a-3i). Reaction conditions: 1 (0.2 mmol), 2a (0.4 mmol), Cu(OCOC<sub>8</sub>H<sub>17</sub>)<sub>2</sub> (10 mol%), DIPEA (0.4 mmol), solvent (2.0 mL), 1 h.



Scheme 3. Synthesis of *N*-arylindole (4b–4h). Reaction conditions: 1 (0.2 mmol), 2 (0.4 mmol), Cu(OCOC<sub>8</sub>H<sub>17</sub>)<sub>2</sub> (10 mol%), DIPEA (0.4 mmol) solvent (2.0 mL), 1 h.



To probe the reaction mechanism, controlled experiments were performed. First, the reaction was operated with omitting of the diaryliodonium triflate, and the material did not react. When **5** was subjected to the reaction under the standard reaction conditions, the desired product **3a** was obtained in 94%

yield (Scheme 5). According to these results, the cascade reaction can be described as follows (Scheme 6). First, the Cu catalyst and diaryliodonium salt generated Cu(III)–aryl, which was demonstrated to be a reactive intermediate. Then this reactive intermediate, which served as an aromatic electrophile, reacted with 2-alkynylaniline to give the *N*-arylation product (5) with the assistance of the base. Finally, heteroannulation took place with the help of the Cu catalyst to afford *N*-arylindole (3).

In conclusion, we developed an efficient Cu catalyzed selective arylation/annulation cascade reaction of 2-alkynylanilines with diaryliodonium salts. The novelty of this strategy lies in giving excellent selectivity of *N*-arylation as opposed to *C*-arylation. Many functional group and diaryliodonium salts



Scheme 5. Control experiments study.



Scheme 6. Mechanism of the cascade reaction.

were tolerated to afford a large scope of *N*-aryl indoles with good to excellent yield. The reaction was shown to be the selective *N*-arylation first and then heteroannulation.

# Acknowledgments

The authors thank Prof. Yonggui Zhou and Dr. Wenxue Huang for chemical reagents and helpful discussions.

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