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Transition-metal-free synthesis of multisubstituted *N*-arylindoles via reaction of arynes and α-amino ketones

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ABSTRACT

A simple transition-metal-free protocol for the synthesis of indoles has been developed using aryne cycloaddition. The in situ-generated arynes couple with α-amino ketones through a one-step *N*-arylation–nucleophilic addition process under mild conditions and efficiently produce multisubstituted *N*-arylindoles.

1. Introduction

The indole skeleton is a privileged structure found in biologically active natural products and pharmaceutically active compounds.[1] Continuous efforts have been exerted to develop alternative methods for the synthesis of this ubiquitous aromatic heterocycle structure.[2] Despite the well-established Fischer indole synthesis,[3] in the past decades, numerous methods based on transition-metal-catalyzed C–C and C–N bond formation reactions have been developed and have provided facile access to indoles and their derivatives.[4] However, the construction of this heterocyclic structure faces a number of challenges, such as the requirement of a stoichiometric amount of transition-metal catalysts or additives, relatively high reaction temperature, and limited scope of the reactions. Hence, the development of an environmentally benign and efficient approach for the synthesis of these compounds is of high importance.

Arynes[5] are highly active intermediates that are widely used in synthetic chemistry; in particular, the annulation of arynes provides convenient access to various pharmaceutically active heterocycles, such as benzisoxazoles,[6] indolines,[7] carbazoles,[8] coumarines,[9] and others.[10] Greaney[11] reported that arynes can undergo a Fischer indole reaction with *N*-tosyl hydrazones to produce *N*-tosylindoles efficiently via a two-step procedure. However, excess $BF_3 \cdot OEt_2$ and reflux conditions are required for the Fischer-cycloaddition. Wang[12] also developed an improved Hemetsberger-indole reaction using arynes and azides, but the products are limited to 2-carboxylated free indoles. We hypothesized that the coupling of arynes with the readily available α-amino ketones would lead to the formation of an indole ring. In this paper, we report an alternative method for the synthesis of multisubstituted *N*-arylindoles.[13] The procedure involves a one-step tandem reaction of arynes under transition-metal-free conditions.

2. Results and discussion

Our study commenced with a cascade reaction of the commercially available aryne precursor **1a** and α-amino ketone **2a** in the presence of 3.0 equiv CsF. The reaction proceeded smoothly in acetonitrile at room temperature and produced *N*-arylindole **3a** in 60% yield (Table 1, entry 1). KF and Bu_4NF were also tested for the reaction, but they only catalyzed the reaction in low efficiency (Table 1, entries 2 and 3). When 3.0 equiv 18-crown-6 was added as a co-additive with 3.0 equiv KF or CsF, the yield of **3a** increased dramatically (Table 1, entries 4 and 5). The suitability of other reaction media, such as THF, toluene, and DCM, was also evaluated. The results indicate that CH_3CN is the optimal solvent in terms of yield (Table 1, entries 6–8). Reducing the additive loading resulted in a dramatic decrease in the reaction yield (Table 1, entries 9–11).

The generality of the reaction was then determined under optimized reaction conditions. As shown in Table 2, various α-amino ketones can couple with arynes to produce the desired

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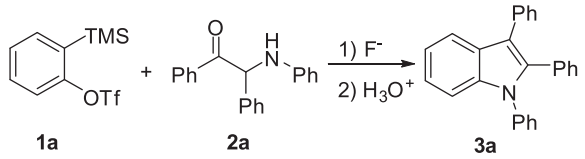
Table 1
Evaluation of reaction conditions[a]

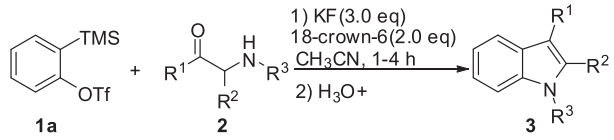


1a 2a 3a

Entry	Additives	Solvent	*t* (h)	Yield[b] (%)
1	CsF 3.0 equiv	CH_3CN	16	60
2	KF 3.0 equiv	CH_3CN	16	12
3	Bu_4NF 3.0 equiv	CH_3CN	13	32
4	CsF+18-crown-6 (3.0 equiv)	CH_3CN	1	93
5	KF+18-crown-6 (3.0 equiv)	CH_3CN	1	97
6	KF+18-crown-6 (3.0 equiv)	THF	4	87
7	KF+18-crown-6 (3.0 equiv)	toluene	4	13
8	KF+18-crown-6 (3.0 equiv)	CH_2Cl_2	4	41
9	KF+18-crown-6 (2.0 equiv)	CH_3CN	6	90
10	KF+18-crown-6 (1.0 equiv)	CH_3CN	26	68
11	No additives	CH_3CN	16	<10

[a] Reaction conditions: **1a** (1.5 equiv), **2a** (0.1 M, 1.0 equiv), room temperature.
[b] Isolated yield.

Table 2
Indole synthesis via aryne cyclization[a]



1a 2 3

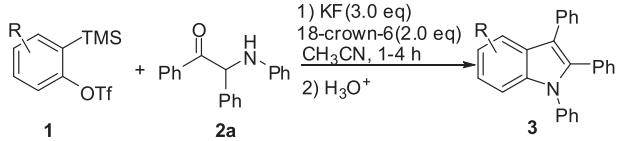
Entry	R^1	R^2	R^3	**3**, Yield[b] (%)
1	Ph	Ph	Ph	**3a**, 97
2	*p*-Cl-Ph	*p*-Cl-Ph	Ph	**3b**, 73
3	*p*-Br-Ph	*p*-Br-Ph	Ph	**3c**, 74
4	Ph	Ph	*p*-Cl-Ph	**3d**, 82
5	*p*-Br-Ph	Ph	Ph	**3e**, 83
6	*p*-Me-Ph	*p*-Me-Ph	Ph	**3f**, 91
7	*p*-MeO-Ph	*p*-MeO-Ph	Ph	**3g**, 85
8	*p*-Me-Ph	*p*-Me-Ph	*p*-MeO-Ph	**3h**, 93
9	Ph	Ph	*p*-Me-Ph	**3i**, 86
10	Ph	Ph	*p*-MeO-Ph	**3j**, 92
11	Ph	*p*-MeO-Ph	Ph	**3k**, 89
12	*p*-Br-Ph	*p*-MeO-Ph	Ph	**3l**, 88
13	*p*-Cl-Ph	*p*-Cl-Ph	*p*-MeO-Ph	**3m**, 86
14	*p*-Br-Ph	*p*-Br-Ph	*p*-MeO-Ph	**3n**, 74
15	Ph	*p*-CF_3-Ph	Ph	**3o**, 88
16	*m*-MeO-Ph	*m*-Br-Ph	Ph	**3p**, 99
17	*m*-Br-Ph	*o*-MeO-Ph	Ph	**3q**, 99
18	2-Furan	Ph	Ph	**3r**, 63
19	2-Furan	*p*-MeO-Ph	Ph	**3s**, 66
20	*p*-Cl-Ph	Me	Ph	**3t**, 72
21	Me	Et	Ph	**3u**, 51
22[c]	Ph	Ph	Ph	**3a**, 95

[a] Reaction conditions: **1a** (0.45 mmol), **2** (0.3 mmol), KF (0.9 mmol), 18-crown-6 (0.9 mmol), anhydrous acetonitrile 3.0 mL, room temperature.
[b] Isolated yield.
[c] Compound **1a** (5.0 mmol), compound **2a** (4.0 mmol), KF (4.0 mmol), 18-crown-6 (4.0 mmol), anhydrous acetonitrile 5.0 mL, room temperature, 13 h.

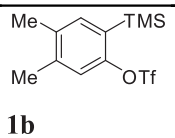
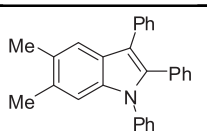
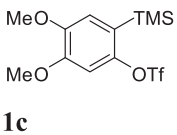
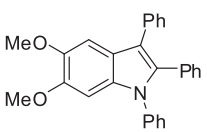
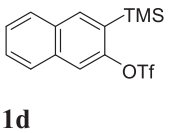
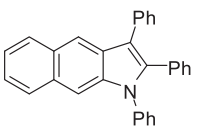
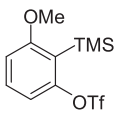
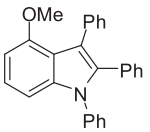
multisubstituted *N*-arylindoles in moderate to high yield (50–99%). Both electron-withdrawing and electron-donating substituents at different positions of the α-amino ketones were suitable for these processes (Table 2, entries 1–17). Interestingly, heteroaryl-substituted *N*-arylindoles can also be obtained in good yield via this coupling reaction (Table 2, entries 17 and 19). α-Alkyl substituted α-amino ketones could be employed as suitable substrates to provide α-alkyl substituted *N*-arylindoles in moderate to good yield (Table 2, entries 20 and 21). The coupling reaction could be conducted on gram-scale and high yield maintained (Table 2, entry 22).

Substituted arynes were also successfully used in the cascade reaction (Table 3). The symmetric arynes derived from precursors **1b**, **1c**, and **1d** efficiently underwent the coupling reaction to afford the corresponding multisubstituted indoles in high yields (Table 3, entries 1–3). Notably, the asymmetric aryne derived from precursor **1e** coupled with α-amino ketone with high regioselectivity and yielded **3x** as the sole product (Table 3, entry 4).[14]

Table 3
Evaluation of substituted arynes[a]



1 2a 3

Entry	1	Product	Yield[b] (%)
1	 **1b**		**3v**, 87
2	 **1c**		**3w**, 88
3	 **1d**		**3x**, 90
4	 **1e**		**3y**, 95

[a] Reaction conditions: **1** (0.45 mmol), **2a** (0.3 mmol), KF (0.9 mmol), 18-crown-6 (0.9 mmol), anhydrous acetonitrile 3.0 mL, room temperature.
[b] Isolated yield.

A plausible mechanism (Scheme 1) was proposed for the coupling reaction of arynes based on the experimental results and pioneering studies.[7] The amino group of the α-amino ketone reacted with the aryne via an insertion reaction and subsequently underwent nucleophilic addition to the ketone to yield a substituted indoline, which was also successfully isolated in high yield.[15] Hydrolysis of indoline under acidic conditions produced the target multisubstituted *N*-arylindole product.

3. Conclusions

In conclusion, we have demonstrated a fluoride-mediated cascade annulation reaction of arynes and α-amino ketones. The efficient, transition-metal-free and extremely mild conditions provide a novel and conscious approach for the synthesis of multisubstituted *N*-arylindoles from readily available substrates.[16] Furthermore, the reaction can be readily scaled up without reducing the reaction yield. Further investigations on the