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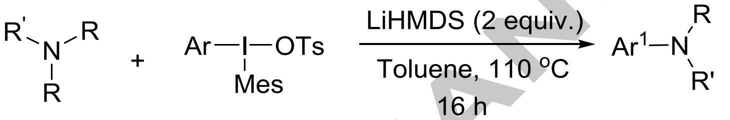

R = alkyl, R' = alkyl, aryl
26 examples
55-91% yields

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ABSTRACT

With a strategy by using diaryliodonium salts as the precursors of benzynes, direct *N*-arylation of tertiary amines with diaryliodonium salts was reported. Thus, the desired aromatic tertiary amines with a wide range of substituents were synthesized in moderate to excellent yields of 55-91%.

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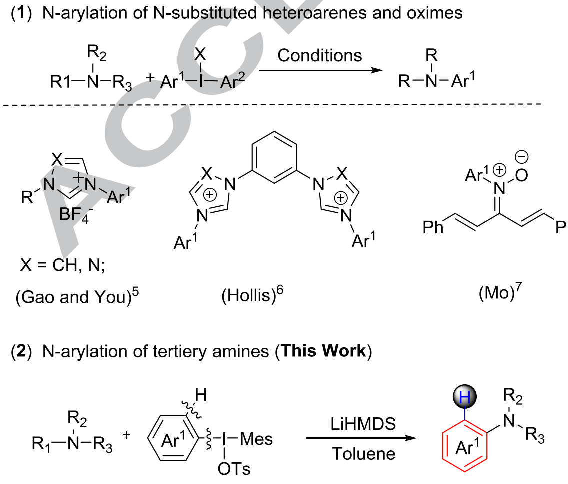
1. Introduction

Direct *N*-arylation, a convenient approach for construction of C(*sp*^{2})-N bonds, has been extensively investigated in the synthesis of aromatic amines.[1] Among them, diaryliodonium salts played an important role in the development of *N*-arylations in an efficient manner.[2] In recent years, direct *N*-arylation of secondary aliphatic amines, aromatic amines, amides, sulfoximines and various *N*-heterocyclic aromatics with diaryliodonium salts had been recorded under mild conditions.[3] In general, the nitrogen containing substrates were employed as *N*-nucleophiles in these reactions, which the *N*-nucleophiles reacted with aryl cations or aryl radicals for producing aryl amines. Since the year of 2012, our group had reported *N*-arylation methodologies in the preparation of *N*-arylcarbazoles, *N*-arylated 1,8-naphthalimides, *N' N*-diarylsulfonamides and *N*-arylated hydroxylamines under metal-catalysis or harsh basic reaction conditions.[4] However, *N*-arylation of substrates containing nitrogen atom without N-H has rarely been reported. For the cases of *N*-heterocyclic aromatics with no N-H bond (Scheme 1, (1)), Gao and You et al. used diaryliodonium salts for directly quaternization of *N*-substituted imidazoles in the synthesis of aryl imidazolium salts as well as aryl triazolium salts in moderate to excellent yields.[5] Later, the research group of Hollis extended this methodology to di-imidazolium systems to obtain diarylated pincer ligand precursors in a single step.[6] Recently, the research group of Mo reported a metal-free *N*-arylation of oximes with diaryliodonium salts to produce *α,β*-unsaturated *N*-aryl ketonitrones under mild conditions.[7] Furthermore, this method of *N*-arylation was attempted to prepare 2,3-quaternary fused indolines in good yields with high diastereoselectivity from alkynyl tethered oximes.[8] In the case of direct aryl quaternization of *N*-alkyl imidazoles, Yoshida and Kunai have reported a methodology by using aryne intermediates in 2002, in which the arynes were generated from a Kobayashi precursor of silylaryl triflate in the presence of CsF.[9] The strategy was widely employed to react with a variety of nitrogen-based nucleophiles.[10] For example, the research group of Biju described a monoselective *N*-arylation of aromatic tertiary amines using a transition-metal-free approach using silylaryl triflate with KF in the presence of crown ether.[11] Very recently, Stuart group and Wang group [12] independently found that benzynes can be generated by simple diaryliodonium salts comparing with the phenyl[*o*-(trimethylsilyl)phenyl]-iodonium triflate by Kitamura in 1995.[13] Inspired by these excellent works, we reported herein a transition-metal-free *N*-arylation of tertiary amines by using diaryliodonium salts as the precursor of benzynes to access aromatic tertiary amines (Scheme 1, (2)).

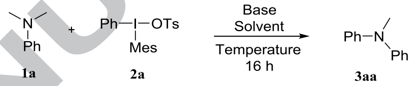


Scheme 1. *N*-arylations with diaryliodonium salts; Mes = 2,4,6-trimethylphenyl. OTs = 4-toluenesulfonate.

2. Results and Discussion

Initially, we used *N,N*-dimethylaniline **1a** and phenyl(mesityl)iodonium tosylate **2a** as starting materials for the optimization of the reaction conditions, the results were shown in Table 1. Screening of several bases showed that LiHMDS was the most suitable base (Table 1, entry 1-11). The desired product **3aa** was afforded in 65% yield, while other bases such as KOH, K_2CO_3, Cs_2CO_3, $NaNH_2$, and NaH proved to be ineffective (Table 1, entries 1-5). The strong bases of KO^{t}Bu, NaO^{t}Bu, NaOMe and KHMDS led to decreased yields of 7-45% (Table 1, entry 6-10). The yield of **3aa** was improved to 70% when the temperature was elevated to 110 °C. We then investigated the influence of the excess of **2a** and LiHMDS on the yield of **3aa**. When two equivalents of **2a** and two equivalents of LiHMDS was used in this reaction, an excellent yield of 91% was achieved (Table 1, entry 14). The solvent effect was also examined, toluene was found to be superior to other solvents such as THF, CH_3CN (Table 1, entries 17 and 18). no desired product was observed in CH_3CN as solvent (Table 1, entry 18).

Table 1. optimization for the Reaction of N,N-dimethylaniline (**1a**) with diaryliodonium salt (**2a**).[a]



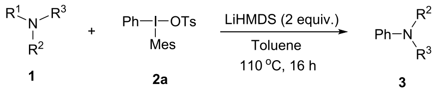
Entry	**2a** (equiv.)	Base (equiv.)	Solvent	Temperature (°C)	Yield (%)[b]
1	1.2	KOH (1)	Toluene	100	0
2	1.2	K_2CO_3 (1)	Toluene	100	0
3	1.2	Cs_2CO_3 (1)	Toluene	100	0
4	1.2	NaH (1)	Toluene	100	0
5	1.2	$NaNH_2$ (1)	Toluene	100	0
6	1.2	KO^{t}Bu (1)	Toluene	100	15
7	1.2	KO^{t}Bu (1.5)	Toluene	100	18
8	1.2	NaO^{t}Bu (1.5)	Toluene	100	7
9	1.2	NaOMe (1.5)	Toluene	100	23
10	1.2	KHMDS (1.5)	Toluene	100	45
11	1.2	LiHMDS (1.5)	Toluene	100	65
12	1.2	LiHMDS (1.5)	Toluene	110	70
13	1.5	LiHMDS (1.5)	Toluene	110	74
14	2	LiHMDS (2)	Toluene	110	91
15	2	LiHMDS (2.5)	Toluene	110	85
16	2.5	LiHMDS (2)	Toluene	110	90
17	2	LiHMDS (2)	THF	60	52
18	2	LiHMDS (2)	MeCN	80	0

[a] Reaction conditions: **1a** (0.4 mmol, 1 equiv.), base (0.4-1 mmol, 1-2.5 equiv.), solvents (4 mL), 16 h. [b] Isolated yields. Mes = 2,4,6-trimethylphenyl. OTs = 4-toluenesulfonate.

With the optimal conditions in hand, we next investigated the scope of the *N*-arylation reaction, as shown in Table 2. A range of tertiary amines **1** was applied in this reaction under the identified optimized conditions. It was found that the electronic properties of substituents on the anilines affected reaction efficiency. For example, anilines with electron-donating

(Me, OMe, ^{i}Pr) groups are well tolerated to give products **3aa-3ag** in good yields of 80-91% (Table 2, entries 1-7). However, the anilines with electron-withdrawing (4-F, 4-CHO) groups gave moderate yields of 63-70% (Table 2, entries 8-9). We also investigated the reactions of *N,N*-diethylaniline and *N,N*-dibutylaniline with diaryliodonium salt **2a**, the reaction afforded the expected products **3aj-3ak** in good yields (Table 2, entries 10-11). As can be seen, the aliphatic tertiary amines such as triethylamine, tripropylamine and tributylamine with diaryliodonium salt **2a** was also examined, the reactions proceeded well under the optimal conditions to give the desired aromatic amines in excellent yields of 68-80% (Table 2, entries 12-14). Furthermore, the reaction of *N*-isobutyl-*N*-methylaniline with diaryliodonium salt **2a** was investigated under the optimal conditions (Table 2, entry 15). The experiments revealed that only the demethylated products **3ao** was obtained in the moderate yield of 76%. Therefore, the results indicated that both aromatic and aliphatic tertiary amines provided desired products in good to excellent yields with this method. However, the arylamines bearing electron withdrawing groups of 4-nitro, 3,5-ditrifluoromethyl were failed to give the desired products (Table 2, entries 16-17).

Table 2. Reaction of tertiary amine **1** with diaryliodonium salt **2a**. [a]

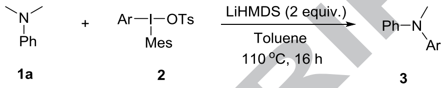


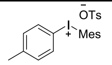
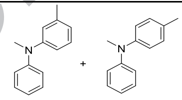
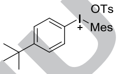
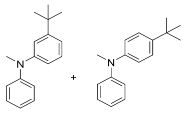
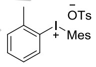
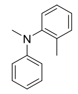
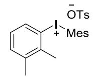
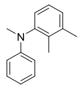
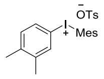
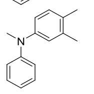
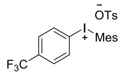
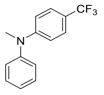
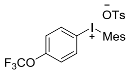
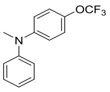
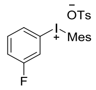
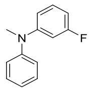
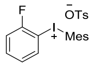
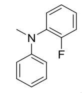
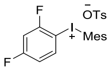
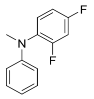
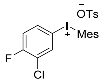
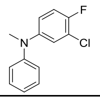
Entry	R^1	R^2	R^3	Product	Yield (%)[b]
1	CH_3-	CH_3-	C_6H_5-	**3aa**	91
2	CH_3-	CH_3-	2-MeC_6H_4-	**3ab**	82
3	CH_3-	CH_3-	3-MeC_6H_4-	**3ac**	80
4	CH_3-	CH_3-	4-MeC_6H_4-	**3ad**	90
5	CH_3-	CH_3-	3-MeOC_6H_4-	**3ae**	83
6	CH_3-	CH_3-	4-MeOC_6H_4-	**3af**	88
7	CH_3-	CH_3-	4-^{i}PrC_6H_4-	**3ag**	89
8	CH_3-	CH_3-	4-CHOC_6H_4-	**3ah**	70
9	CH_3-	CH_3-	4-FC_6H_4-	**3ai**	63
10	Et-	Et-	C_6H_5-	**3aj**	81
11	^{n}Bu-	^{n}Bu-	C_6H_5-	**3ak**	75
12[c]	Et-	Et-	Et-	**3al**	68
13	^{n}Pr-	^{n}Pr-	^{n}Pr-	**3am**	80
14	^{n}Bu-	^{n}Bu-	^{n}Bu-	**3an**	75
15	CH_3-	^{i}Bu-	C_6H_5-	**3ao**	76
16	CH_3-	CH_3-	4-$NO_2C_6H_4$-	**3ap**	0
17	CH_3-	CH_3-	3,5-$(CF_3)_2C_6H_3$-	**3aq**	0

[a] Reaction conditions: **1** (0.4 mmol), **2a** (0.8 mmol, 2 equiv.), LiHMDS (1M in THF, 0.8 mL, 2 equiv.), Toluene (4 mL), 110 °C, 16 h. [b] Isolated yields. [c] **1** (0.8 mmol, 2 equiv.), **2a** (0.4 mmol). Mes = 2,4,6-trimethylphenyl. OTs = 4-toluenesulfonate.

To further explore the generality of this reaction, the scope of aryl(mesityl)iodonium salts **2** was also examined (Table 3). The reaction of *N, N*-dimethylaniline **1a** with a variety of substituted diaryliodonium salts **2** were conducted under the optimal conditions. We investigated the steric and electronic effects on the *N*-arylation reaction. As shown in Table 3, when iodonium salts **2** have electron-donating (Me, ^{t}Bu) groups on the aryl moiety the reaction gave the desired products **3ba-3be** in excellent yields of 80-90% (Table 3, entries 1-5); In the cases of **3ba** and **3bb**, both two isomers in different ratio were determined by ^{1}H NMR spectra according to the formed benzyne intermediates. the regioisomeric products were not separable by column chromatography on silica gel. However, only one isomer of **3be** was obtained as suggested by NMR spectra, which might be due to the steric effect. The diaryliodonium salts with electron-withdrawing groups (4-F, 4-CF_3, 4-OCF_3) only give the moderate yields of 55-67% (Table 3, entries 6-11). The results indicated that diaryliodonium salts with electron-donating groups favored this reaction. Interestingly, only one isomer was obtained in these cases of **3bf**, **3bg, 3bh** and **3bk** (Table3, entries 6-11).

Table 3. Reaction of *N,N*-dimethylaniline **1a** with diaryliodonium salts **2**. [a]

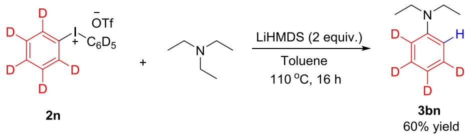


Entry	2	3	The structures of 3	Yield (%)[b]
1[c]		**3ba**	 meta/para = 6 : 5	89
2[c]		**3bb**	 meta/para = 3 : 2	87
3		**3bc**		84
4		**3bd**		80
5		**3be**		90
6		**3bf**		55
7		**3bg**		71
8		**3bh**		65
9		**3bi**		67
10		**3bj**		58
11		**3bk**		61

[a] Reaction conditions: **1** (0.4 mmol), **2a** (0.8 mmol, 2 equiv.), LiHMDS (1M in THF, 0.8 mL, 2 equiv.), Toluene (4 mL), 110 °C, 16 h. [b] Isolated yields. [c] The ratio of two isomers was determined by ^{1}H NMR spectroscopy. Mes = 2,4,6-trimethylphenyl. OTs = 4-toluenesulfonate.

To further validate the mechanism of the reaction, we used a deuterated diaryliodonium salt **2n** as the reactant for the arylation with triethylamine (Scheme 2). We observed a deuterium at the *ortho*-phenyl carbon was replaced by a proton. This experiment suggested that the benzyne intermediate was formed during the reaction process. We therefore proposed a possible mechanism of the reaction as shown in Figure 1. First of all, the diaryliodonium salt generated benzyne intermediate under the condition of alkali, and then triethylamine as the nucleophile attacks the benzyne intermediate to generate amphoteric ion intermediate.

Finally the Zwitterionic intermediate undergoes a proton transfer to form the desired product and a molecule of ethylene.



Scheme 2. A deuterated diaryliodonium salt was involved in the reaction with triethylamine.

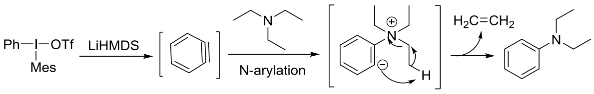


Figure 1. Plausible reaction mechanism.

3. Conclusions

In conclusion, we have developed a direct *N*-arylation of aromatic and aliphatic tertiary amines with diaryliodonium salts under transition-metal-free conditions. A variety of tertiary amines and diaryliodonium salts proceeded well and afforded the desire aromatic tertiary amines in excellent yields of 55-91%. The experimental results indicated that the diaryliodonium salts transform into benzyne during the reaction process. Therefore, this method also provides a new way for the synthesis of aromatic amines

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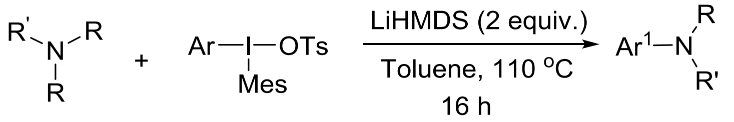
Highlights

- A synthetic method of *N*-arylation of tertiary amines via benzynes with diaryliodonium salts was developed.
- The desire aromatic tertiary amines were synthesized in good yields of 55-91%.
- Diaryliodonium salts was used as the precursors of benzynes.



R = alkyl, R' = alkyl, aryl
26 examples
55-91% yields