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Communication

Cu-catalyzed arylation of 1-acyl-1*H*-1,2,3-Benzotriazoles via C–N activation

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ABSTRACT

An efficient copper-catalyzed arylation reaction of 1-acyl-1*H*-1,2,3-benzotriazoles with diaryliodonium salts via C–N activation is explored. The reaction is conducted regioselectively to form 1-aryl-1*H*-1,2,3-benzotriazoles in MeCN at 80 °C in the presence of cesium carbonate. 29 examples are given with the product yield of up to 84%. The probable reaction mechanism is proposed.

1. Introduction

Nitrogen-containing heterocycles are subunits found in numerous natural products and in many biologically active pharmaceuticals [1]. N1-Modified benzotriazoles are important nitrogen-containing heterocyclic compounds, many of which possess biological and pharmacological activity [2–5]. They can be used as anti-inflammatory, anti-tumor, anti-depressant, anti-fungal, anti-malarial and other drugs [6–9], as well as has broad applications in fine chemicals [10] and materials science [11]. Although copper catalyzed Ullmann-type C–N bond formation reaction is an important, straightforward and inexpensive approach to synthesize nitrogen-containing heterocycles, it has some disadvantages. For example, the reaction usually requires severe conditions of temperature higher than 200 °C, excess nucleophiles, longer reaction time, the strong bases and a stoichiometric amount of copper activator [12]. Therefore a highly efficient, mild C–N bond construction method has been paid much attention by chemists.

Arylation reaction is an important way for the modification of 1*H*-1,2,3-benzotriazoles to prepare 1-aryl-1*H*-1,2,3-benzotriazoles, which has found wide applications not only in synthetic organic chemistry but also in biological [13], medicine [14], materials [15] and other aspects. The new C–N bond formation method from 1*H* to 1,2,3-benzotriazoles was focused on the use of various arylating reagents. Aryl halides were the first arylating reagents reported in the preparation of 1-aryl-1*H*-1,2,3-benzotriazoles (Scheme 1a) [16,17]. In 2017, Hashem Sharghi and coworkers used phenylboronic acid as an arylating reagent to achieve Cu(II)-catalyzed N1-phenylation reaction of 1*H*-1,2,3-benzotriazole under solvent-free conditions (Scheme 1b) [18].

Due to their versatile character, commercial availability, environmental-friendly behavior and enormous potential in C–C and C-heteroatom coupling, diaryliodonium salts have afforded efficient arylation of diverse nucleophiles, in particular heteroatom nucleophiles [19]. In 1998, Beletskaya and coworkers reported six examples of Pd(II) and Cu(II) salts co-catalyzed 1-arylation reaction of 1*H*-1,2,3-benzotriazoles with diaryliodonium salts to prepare 1-aryl-1*H*-1,2,3-benzotriazoles [20]. Lately, they found that Pd/Al_2O_3 could catalyze this reaction successfully [21]. Kang research group [22] also used $Cu(acac)_2$ as an efficient catalyst to accomplish N-arylation of benzotriazole with diaryliodoniums (Scheme 1c).

With our continuous investigation on high efficient arylation reaction using diaryliodonium salts as arylating reagents, we report herein copper-catalyzed regioselective arylation reaction of 1-acyl-1*H*-1,2,3-benzotriazoles with diaryliodonium salts via C–N activation to form 1-aryl-1*H*-1,2,3-benzotriazoles, which involves

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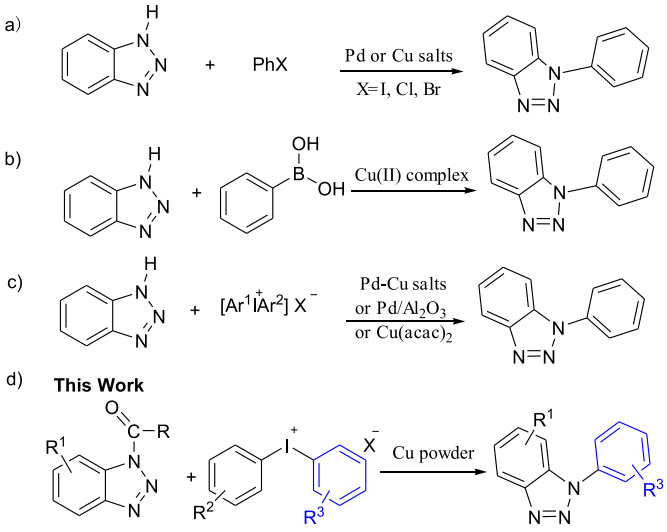
0022-328X/



Scheme 1. Methods for the synthesis of 1-aryl-1*H*-1,2,3-benzotriazoles.

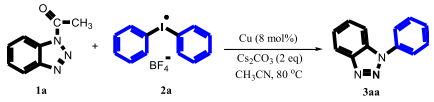
tandem amide C–N bond cleavaging and a new C–N bond formation (Scheme 1d).

2. Results and discussion

The reaction conditions were first optimized using 1-acetyl-1*H*-1,2,3-benzotriazole (**1a**) and diphenyliodonium tetrafluoroborate (**2a**) as model substrates and the results are listed in Table 1. With 8 mol% of commercial copper powder as a catalyst and cesium carbonate as a base, the reaction was conducted in acetonitrile at 80 °C for 24 h and the product of 1-phenyl-1*H*-1,2,3-benzotriazole (**3aa**) was obtained in 83% yield (entry 1). Only trace of N2-arylation product was observed. When using Cu_2O as the reaction catalyst, good yield of the desired product **3aa** of 77% was obtained (entry 2). So we deduced that Cu(I) may be beneficial for this catalytic reaction and Cu(I) halides (halide = Cl, Br and I) were used as catalysts and medium to good yields (60%, 63% and 75%, respectively) were achieved (entries 3–5). However, when using palladium compounds as catalysts instead of copper powder, the product yield showed significant decrease to 36% and 44%, respectively (entries 6 and 7). These indicate that copper has better catalytic activity than palladium in this reaction. Treatment of **1a** with **2a** using potassium carbonate as a base and copper powder as a catalyst in CH_3CN affords only 63% yield of **3aa** (entry 8). In the absence of any catalyst or base, trace of the aimed product was observed (entries 9 and 10). The effect of solvents on this reaction was also examined. When the reaction was conducted in N-methylpyrrolidone (NMP), in 1,2-dichloroethane (DCE) and in dimethyl sulfoxide (DMSO), an inferior **3aa** yield of 46%, 74% and 52% than in acetonitrile was obtained, respectively (entries 11–13). The reaction temperature is also sensitive for this transformation. When the reaction temperature was decreased from 80 °C to 50 °C, the product yield was declined dramatically from 82% to 54% even if prolonged the reaction time to 36 h (entry 14). Similarly, when the reaction temperature was arisen to 100 °C in a sealed tube, only 76% of yield was obtained (entry 15). A nitrogen-containing ligand N^2,N^2-diisopropyloxalo-hydrazide ligand which was proved to be efficient in Cu-catalyzed C–N coupling reaction [23] was added into this reaction to improve the product yield, but it did not work (entry 16). We also tried to increase the amount of the catalyst and the alkali to make the yield better, but it was 84% and 83%, respectively and did not change significantly (entries 17 and 18).

With the optimized reaction conditions established, we examined the substrate scope of 1-acyl-1*H*-1,2,3- benzotriazoles in the reaction with **2a**. The results are summarized in Table 2. It is found that this reaction can tolerate a variety of substituents on the benzene ring of benzotriazoles. Reactions of substrate **1** containing an electron-donating (e.g., methyl) or electron-withdrawing (e.g., nitro and chloro) groups worked well to deliver the corresponding products **3ba**-**3ea** in 64%–77% yields. The effect of acyl groups on the reaction is significant. Acetyl group (R = CH_3) led to good product yield of this reaction. With the carbon atom number of chain acyl group increasing, the product yield decreased drastically from 43% of **3fa** to no reaction with valeyl group (R = n-C_4H_9). The steric hindrance of acyl groups is also a key factor in this reaction. When R was benzyl group, the yield was 38%; however, when R was

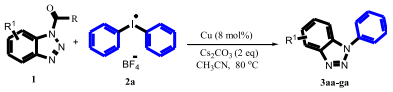
Table 1
Optimization of reaction conditions.[a]



Entry	Catalyst	Base	Solvent	Yield (%)
1	Cu	Cs_2CO_3	CH_3CN	83
2	Cu2O	Cs_2CO_3	CH_3CN	77
3	CuCl	Cs_2CO_3	CH_3CN	60
4	CuBr	Cs_2CO_3	CH_3CN	63
5	CuI	Cs_2CO_3	CH_3CN	75
6	$Pd(OAc)_2$,	Cs_2CO_3	CH_3CN	36
7	PdCl2	Cs_2CO_3	CH_3CN	44
8	Cu	K_2CO_3	CH_3CN	63
9	–	Cs_2CO_3	CH_3CN	trace
10	Cu	–	CH_3CN	trace
11	Cu	Cs_2CO_3	NMP	46
12	Cu	Cs_2CO_3	DCE	74
13	Cu	Cs_2CO_3	DMSO	52
14[b]	Cu	Cs_2CO_3	CH_3CN	54
15[c]	Cu	Cs_2CO_3	CH_3CN	76
16	Cu	Cs_2CO_3/L	CH_3CN	82
17[d]	Cu	Cs_2CO_3	CH_3CN	84
18[e]	Cu	Cs_2CO_3	CH_3CN	83

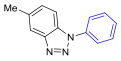
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), Cu (8 mol %), Cs_2CO_3 (2 eq), solvent (3 mL) at 80 °C for 24 h. Yield is isolated yield. L = N^2,N^2'-diisopropyloxalohydrazide.
[b] The reaction is conducted at 50 °C for 36 h.
[c] The reaction temperature is 100 °C.
[d] The amount of Cu powder is 15 mol%.
[e] The dosage of Cs_2CO_3 is 3 equivalents.

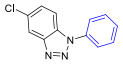
Table 2
Scope of 1-acyl-1*H*-1,2,3-benzotriazoles.[a]

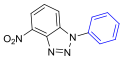


R = CH_3


3aa, 83%


3ba, 74%


3ca, 77%


3da, 73%


3ea, 65%

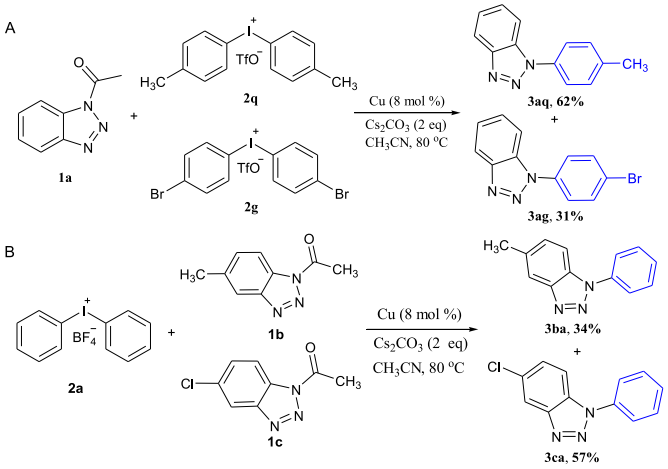

R = CH_3CH_2, **3fa** = **3aa**, 43%
R = n-C_4H_9, n.r.
R = $PhCH_2$, **3ga** = **3aa**, 38%
R = Ph, n.r.
R = 1-naphthyl, n.r.

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), Cu (8 mol%), Cs_2CO_3 (2 eq) in 3 mL of solvent at 80 °C for 24 h. Isolated yield is given. n.r. is no reaction.

phenyl and 1-naphthyl, no corresponding products were obtained.

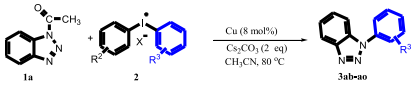
Inspired by the successful Cu-catalyzed arylation of 1-acyl-1*H*-1,2,3-benzotriazoles with diphenyliodonium tetrafluoroborate, a variety of symmetric and unsymmetric diaryliodonium salts as arylating reagents of **1a** were explored in this reaction. The results are listed in Table 3. In comparison with BF_4^-, when TfO^- was used as an anion of diphenyliodonium salts, the yield of the product decreased to 72%; whereas PF_6^- as an anion instead of BF_4^-, no reaction was occurred (**3 ab** and **3ac**). However, when 1a was treated with di(4-(tert-butylphenyl)iodonium hexafluorophosphate, 72% of product yield was obtained (**3ad**). These results show that the reactivity of diaryliodonium salts is related not only to the structure of aryl groups, but also to the type of anions. Symmetric diaryliodonium salts containing electron-donating groups (e.g., methyl, tert-butyl and methoxyl) attached to the benzene ring afforded corresponding arylation products with good yield ranging from 72% to 78% (**3ad**-**3af**). However, electron-withdrawing groups of Br and CF_3 connected to the benzene ring of symmetric diaryliodonium salts led to reduced product yields of 69% and 54%, respectively (**3 ag** and **3ah**). For the reactions of unsymmetric diaryliodonium salts with **1a**, to our delight, good selectivity with synthetically useful yield were obtained. Both electron-donating and electron-withdrawing substituents were tolerated under the reaction conditions and moderate yields of 43%–67% were achieved (**3ai**-**3an**). Diaryliodonium salt containing a heterocyclic aryl was also examined. The reaction of phenyl(2-thienyl)iodonium triflate with 1a proceeded smoothly to yield 43% of 1-(2-thienyl)-1,2,3-benzotriazole deacylation arylation product (**3ao**).

To better understand the substitution effect of different functional groups, competitive reactions were carried out (Scheme 2A). When **1a** was allowed to react simultaneously with (4-methylphenyl)phenyliodonium triflate (**2q**) and (4-bromophenyl) phenyliodonium triflate (**2g**), 1-(p-tolyl)-1*H*-1,2,3-benzotriazole (**3aq**) and 1-(4-bromophenyl)-1*H*-1,2,3-benzotriazole (**3 ag**) were isolated in 62% and 31% yields, respectively. This indicates that an electron-donating group on the diaryliodonium salts reacted more easily than an electron-withdrawing group [20,21]. It may be the reason that in situ formation of electron-deficient aryl Cu(III) intermediate is the key step and electron-rich aryl groups can

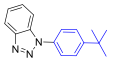


Scheme 2. Competition experiments.

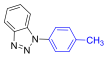
Table 3
Scope of diaryliodonium salts.[a]



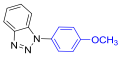
$R^2 = R^3 = H$; X = OTf;
3 ab = **3aa**, 72%
$R^2 = R^3 = H$; X = PF_6;
3ac, n.r.



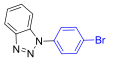
$R^2 = R^3$ = 4-t-Bu;
X = PF_6, **3ad**, 72%



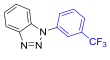
$R^2 = R^3$ = 4-Me;
X = BF_4; **3ae**, 73%



$R^2 = R^3$ = 4-CH_3O;
X = BF_4; **3af**, 78%

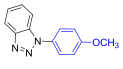


$R^2 = R^3$ = 4-Br;
X = OTf; **3 ag**, 69%

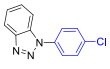


$R^2 = R^3$ = 3-CF_3;
X = BF_4; **3ah**, 54%

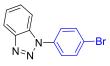
R^2 = H, R^3 = 2-Me;
X = BF_4; **3ai**, 66%[b]



R^2 = H, R^3 = 4-CH_3O; X = BF_4;
3aj = **3af**, 67%[b]

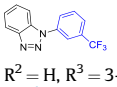


R^2 = H, R^3 = 4-Cl;
X = OTf; **3ak**, 54%[b]



R^2 = H, R^3 = 4-Br; X = OTf; **3 al** = **3 ag**, 57%[b]

R^2 = H, R^3 = 2-Cl; X = BF_4; **3am**, 50%[b]



R^2 = H, R^3 = 3-CF_3; X = BF_4; **3an** = **3ah**, 43%[b]

Phenyl(2-thienyl)iodonium triflate; **3ao**, 43%[b]

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), Cu (8 mol%), Cs_2CO_3 (2 eq) in 3 mL of acetonitrile at 80 °C for 24 h. Isolated yield is given. n.r. is no reaction.
[b] **3aa** was obtained in trace amount or not more than 10% yield.

stabilize this intermediate. Another competitive reaction of diphenyliodonium tetrafluoroborate with **1b** and **1c** afforded **3ba** and **3ca** in 34% and 57% yields, respectively (Scheme 2B). Thus, the presence of an electron-withdrawing group on the benzene ring of benzotriazoles favored the reaction than an electron-donating group. The cause is attributed to the increase of acidcity of NH when bearing an electron-withdrawing group on benzotriazoles.

In order to further study the mechanism, we conducted control experiments (Scheme 3). The results show that the reaction is carried out upon two-step tandem reactions of N-deacylation to generate 1*H*-1,2,3-benzotriazole in 96% yield and then N-arylation to deliver **3aa** in 89% yield under one-pot conditions.

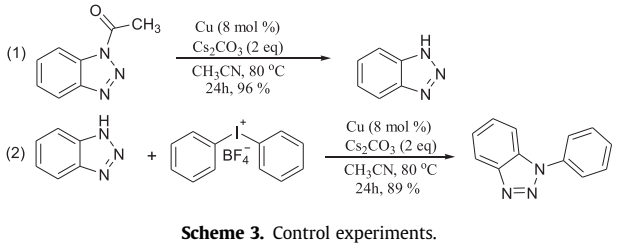
Based on these results, a possible reaction mechanism of 1-acyl-1*H*-1,2,3-benzotriazoles with diaryliodonium was deduced (Scheme 4). First, Cu powder was oxidized to Cu(I) species. Oxidative addition of the diaryliodinium salt **2a** to Cu(I) can generate the highly electrophilic Cu^{III}-aryl intermediate **A** by cleavage of the hypervalentiodine aryl bond. Then, 1-acetyl-benzotriazole undergoes electrophilic attack under the presence of cesium carbonate to form nitrogen anions intermediate **B**. Subsequently, nucleophilic substitution is initiated between intermediates **A** and **B** to form N1-metallation benzotriazole **C**, which is further converted into the aimed product **3aa** upon reductive elimination. Cu(I) species is released to participate in the next catalytic cycle.

3. Conclusion

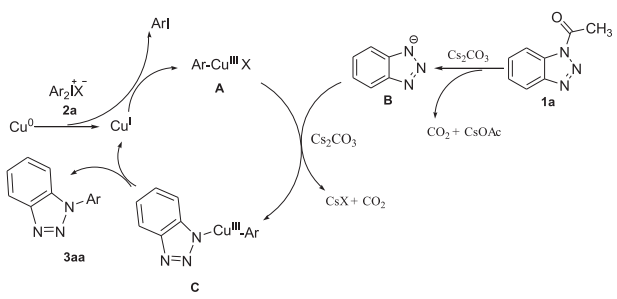
In summary, we have developed a one-pot approach to the synthesis of 1-arylbenzotriazoles by Cu-catalyzed reaction of 1-acyl-1*H*-1,2,3-benzotriazoles with diaryliodonium salts via C–N activation. The method tolerates diverse functional groups and is a feasible and alternative arylation method. The major advantages of this method includes: cheap and commercial easily available copper powder catalysis, wide substrate scope, mild reaction conditions and good step-economy.

4. Experimental

A catalyst (8 mol%), 1-acyl-1*H*-1,2,3-benzotriazoles (0.2 mmol), Cs_2CO_3 (0.4 mmol), diaryliodonium salts (0.4 mmol) and acetonitrile (3.0 mL) were sequentially added into a 25 mL round-bottom flask, and the mixture was stirred in a preheated oil bath at 80 °C for 24 h. Then the resulting mixture was cooled to r.t. and the solvent was removed in vacuum. The crude product was purified by column chromatography on silica gel with ethyl acetate/petroleum ether (1:10 vol) as an eluent to give the desired 1-aryl-1*H*-1,2,3-benzotriazoles.



Scheme 3. Control experiments.



Scheme 4. Probable reaction mechanism.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jorganchem.2019.05.013.

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