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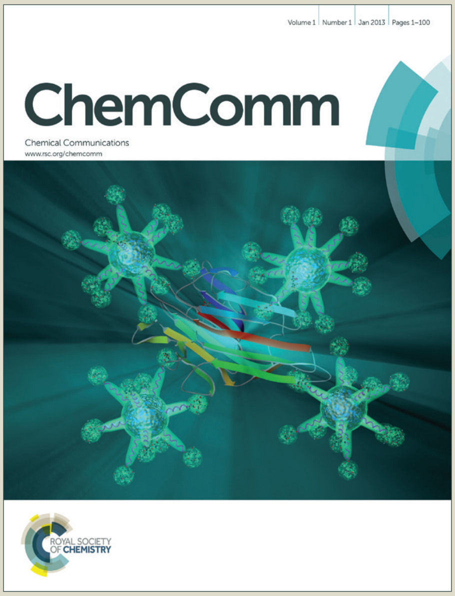

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ARTICLE TYPE

Room-temperature Cu(II)-catalyzed aromatic C-H azidation for the synthesis of ortho-azido anilines with excellent regioselectivity

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Cu(II)-catalyzed aromatic C-H azidation with azido-benziodoxolone under mild condition have been described. The primary amine exhibits excellent ortho-directing effect, providing ortho-azidation anilines as the sole products.

Beside the important roles in the click chemistry of cycloaddition, aromatic azides are also well known for providing an electron-deficient nitrene species, which is able to insert into a C-H bond. Thus, aryl azides have found numerous biological and industrial applications, such as the construction of N-containing structural motifs in drug discovery,[1] photoaffinity labelling reagents in structural proteomics,[2] cross-linkers for high-performance polymer materials,[3] and photografting on polymer surfaces. [4]

Although numerous approaches for the synthesis of aliphatic azides are available, the preparation methods of aryl azides are still limited. The conventional methods for constructing aryl azides involves classical direct nucleophilic aromatic substitution (S_NAr) of activated aryl halides or sulfonates with NaN_3,[5] diazotization of aryl amine with $NaNO_2$ at low temperature under strong acidic conditions and subsequent treatment with azide ion,[6] or the cross-coupling of aryl boronic acids with an azide source such as TfN_3 and NaN_3.[7] Although powerful, these transformations suffer from long reaction time, harsh acidic or basic conditions, oxidative reagent, which are not compatible with many functional groups present in a substrate. What needs to be pointed out is that the direct C-H azidation on aromatic rings to obtain aryl azides under mild conditions have been gradually realized, making it a much more ideal and straight-forward azidation process. Recently, K. A Sasane et al disclosed a sonication-mediated C-H azidation on aryl derivatives through a Friedel-Crafts reaction process.[8] N. Jiao et al developed a Cu(I)-catalyzed regioselective C-H azidation of anilines.[9] X. Li et al described Rh(III)-catalyzed C-H azidation of arene, in which pyridine acted as an efficient directing group.[10] However, the hazardous azide sources, such as NaN_3, or $TMSN_3$ still used in these reactions, are deterrents to their practical applications.

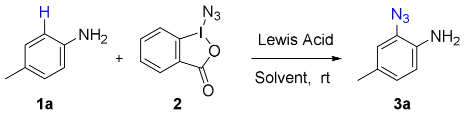
Azides of polyvalent iodine, such as, $PhI(N_3)OAc$ or $PhI(N_3)_2$, generated in suit from the combinations of PhIO or $PhI(OAc)_2$ with $TMSN_3$ or NaN_3, were found to be reactive intermediates in radical-based aliphatic C-H azidation reaction.[11] However, the unstability and high reactivity of these azidoiodinanes have restricted their practical applications as efficient reagents for the introduction of the azido function into organic molecules. Five-membered heterocyclic azidoiodines as novel azidating reagents are found to exhibit high thermal and storage stabilities.[12] So far, however, only a few reports on these azidobenziodoxoles as an efficient azidating regent have been reported.[13] To the best of our knowledge, there is no report on the aromatic C-H azidation based on the thermal stable azidobenziodoxoles.

Herein, we disclose a mild, simple, highly efficient protocol for the diverse synthesis of aryl azides through C-H azidation of anilines catalyzed by less expensive $Cu(OAc)_2$, in comparison with copper(I) salts, at ambient temperature. The thermal stable azidobenziodoxolone as a reliable azide source was first applied in the metal-catalyzed aromatic azide formation. The amino group is found to play an ortho-directing effect in the azidation reactions, regioselectively affording the mono-azidated derivative.

In the initial studies, the azidation of 4-methyl aniline (**1a**) with azidoiodine reagent **2** as a model was carried out to optimize the reaction conditions (Safety notes for using azidobenziodoxolone see Supporting Information). As shown in Table 1, Lewis acid as catalyst was found to be important to initiate the azidation (entry 1). A survey of the catalysts revealed that Cu(I) halide or acetate could give good yields when CH_3CN was used as solvent at room temperature (entry 2-5). $Fe(ClO_4)_3$ and $Zn(ClO_4)_2{\cdot}6H_2O$ were ineffective in the azidation (entry 6, 7), while ZnI_2, $ZnCl_2$, $FeCl_3$, $CuCl_2$ and $CuSO_4$ afforded the desired products with moderate yields (entry 8-11, see Table S1 for studies using other Lewis acids in SI). The $Cu(OAc)_2$ appeared to give better result and acceptable yield (up to 72%) of **3a** (entry 12). It was found that reactions carried out in a range of solvents produced the desired products in good yields, while THF provided the best result (entry 14). However, the reaction did not work when the polar protic solvent of MeOH was used (entry 15). Increasing the catalyst loading from 10% to 20% significantly improved the catalyst performance, providing azidation product in 85% yield (entry 16). Elevated temperature only gave a slightly higher yield without remarkable decrease of reaction time (entry 17). When the molar ratio of the aniline and azidoiodine (III) **2** was applied to 1:1, diazidated product of 2,6-diazidoaniline was also obtained in a total yield of 73% with a mono/di ratio of 3.5:1 (entry 18). To our delight, the molar ratio of the aniline and azidoiodine (III) reagent **2** conducted in 2:1 produced 2-azidoaniline as the sole product with trace of diazidation and by-product in this condition. The excess of aniline could be recovered.

With the optimized reaction conditions established (entry 16), the scope and functional-group tolerance of this Cu(II)-catalyzed azidation reaction were investigated (Table 2).

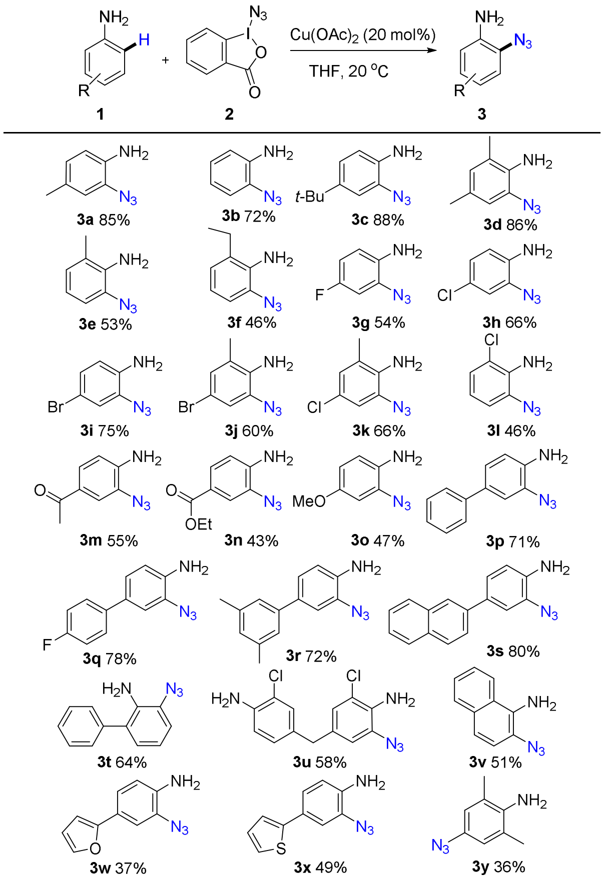
Table 1. Optimization of reaction conditions [a]



Entry	**1a** (equiv)	Lewis acid (mol %)	Solvent	T (°C)	Yield[b]
1	1.0	none	CH_3CN	20	0
2	2	CuI (10)	CH_3CN	20	67
3	2	CuBr (10)	CH_3CN	20	59
4	2	CuCl (10)	CH_3CN	20	57
5	2	CuOAc(10)	CH_3CN	20	52
6	2	$Fe(ClO_4)_3$ (10)	CH_3CN	20	0
7	2	$Zn(ClO_4)_2\cdot 6H_2O$ (10)	CH_3CN	20	0
8	2	ZnI_2 (10)	CH_3CN	20	63
9	2	$ZnCl_2$ (10)	CH_3CN	20	57
10	2	$CuCl_2$ (10)	CH_3CN	20	45
11	2	$CuSO_4$ (10)	CH_3CN	20	57
12	2	$Cu(OAc)_2$ (10)	CH_3CN	20	72
13	2	$Cu(OAc)_2$ (10)	CH_2Cl_2	20	69
14	2	$Cu(OAc)_2$ (10)	THF	20	79
15	2	$Cu(OAc)_2$ (10)	MeOH	20	0
16	2	$Cu(OAc)_2$ (20)	THF	20	85
17	2	$Cu(OAc)_2$ (20)	THF	30	86
18	1.0	$Cu(OAc)_2$ (20)	THF	20	57

[a] Reagent **2** (0.3 mmol), 4-methyl aniline, catalyst, solvent, temperature and indicated solvents under N_2. [b] Isolated yield.

Table 2. Screening results of azidation reaction to ortho-azido anilines

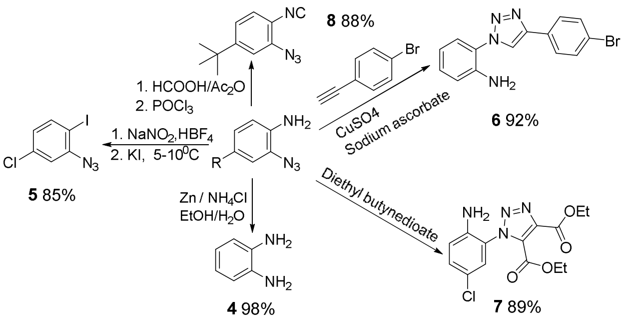


Aryl amines with inert alkyl substituents underwent smooth azidation to afford the desired ortho-substituted products in moderate to high yields (**3a**-**3f**). The substitution pattern of the aromatic ring was found to have apparent influence on the reaction efficiency, with para-substituted substrates working more efficiently to provide the desired product in higher yields (**3a**, **3c**, **3d**). Functionalities such as alkoxy, halide, acetyl, and ester, which serve as useful reaction handles for further elaborations, were well-tolerated under the mild reaction condition (**3g**-**3o**). Note that the substrate with a Br group, which has been shown to be a prominent leaving group in a variety of transition-metal-catalyzed cross-coupling, also underwent smooth azidation to afford the desired azides in good yields (**3i**, **3j**). Interestingly, high azidation efficiency was also observed for the biaryl and fused aromatic substrates, affording the respective azidation products in good to high yield (**3p**-**3v**). Diamino-containing substrate produced the corresponding mono-azidation product **3u** in moderate yield. The heterocycle-containing anilines **3w** and **3x** were found to be viable substrates albeit giving acceptable yields. It should be emphasized that azidation was found to take place only on the amino-containing aromatic rings. The para-azidation reaction was observed when *o,o*'-dimethyl aniline **2y** was employed, affording 36% isolated yield (**3y**) with a large amount of starting material remained.

The synthetic utility was further demonstrated by performing the chemical modification of the *o*-azido anilines. As shown in Scheme 1, azidation reduction was achieved by treatment with Zn/NH_4Cl in reflux EtOH, providing almost stoichiometric 1,2-diamino benzene **4**.[14a] By means of the well-known Sandmeyer reaction, diazotization of **3h** with *t*-butyl nitrite, followed by treatment with KI, produced 2-azido-4-chloro-1-iodobenzene **5** in high yield.[14b] As expected, **3b** or **3h** was suitable substrate for a Cu-catalyzed [3+2] alkyne/azide cycloaddition, giving trizoles **6**, **7** in excellent yields.[14c] N-formylation of the 2-azido aniline **3c**, followed by dehydration, providing 2-azido-1-isocyanobenzene **8**, which is an important precursor in the template-controlled synthesis of NH, NH-NHC complexes.[14d]

In order to gain insight into the role of amino group, the effect of substituent on amino group was investigated. Though a primary amino-directed ortho azidation reaction was found to proceed well, a complex mixture was given when the secondary amine of N-phenyl aniline or N-methyl aniline were applied in the azidation reaction. No conversion was observed for N-acetyl aniline, N,N-dimethyl aniline and phenylmethanamine under the standard conditions. These results demonstrated that a free amino group on anilines is required for this azidation.

Preliminary studies on the mechanism was performed, using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and hydro-quinone (HQ) separately as radical scavengers in the reaction of



Scheme 1. Functionalization of ortho-azido anilines

aniline and azidoiodine (III) reagent **2**. The azidation reaction was completely inhibited, indicating that a radical process may be involved in this reaction. Further GC-MS analysis confirmed the formation of TEMPO-N_3 (see the SI). This result is consistent with the literature data on radical mechanism for aliphatic C-H azidations by the unstable azidoiodinanes, $PhI(N_3)OTMS$, $PhI(N_3)_2$,[15] and the report on the stable azidobenziodoxoles. However, in contrast with the previously reported aliphatic C-H azidation with azidobenziodoxolone **2** in presence of radical initiator at high reaction temperature,[12] the Cu(II)-catalyzed aromatic C-H azidation by reagent **2** in this work proceeded well in absence of any radical initiator under very mild reaction condition, providing the ortho-azidation products in good yields.

On the basis of this result in hand, a plausible working hypothesis is proposed for the reaction mechanism (Scheme 2). It is assumed that initial one-electron oxidation of aniline by oxidative hypervalent iodine (III) reagent **2** results in the formation of aniline radical cation and radical anion **A**.[16] Rapid collapse of radical anion **A** would undergo a Lewis acid catalyzed bond cleavage, producing N_3-containing 2-iodo-benzoate **B**. Decomposition of **B** gives copper(II) salt **C**, with simultaneous release of a relatively stable azide radical. The N_3 radical preferentially attacks the aromatic ring ortho to the primary amino group of the aniline radical cation, regioselectively generating the cyclohexadienyl cation species **D**. Finally, deprotonation of **E** by 2-iodobenzoate **C** could afford the desired azidation product **3**. The generated 2-iodobenzoic acid **F** in the last step was also detected by ^1H NMR spectroscopy. Further investigation will be required to elucidate the nature of the C-H azidation reaction in this work, though a SET process proposed for the reaction mechanism under the present study is more probable.

In conclusion, we have described a mild procedure of aromatic C-H azidation with azidobenziodoxolone **2** catalyzed by cheap $Cu(OAc)_2$. With the efficient ortho-directing effect of the primary amino group, the reactions exhibit a unique regioselectivity in that ortho-azidation is strongly preferred. This azidation procedure provides an easy access for further chemical modifications of the ortho-azido anilines.

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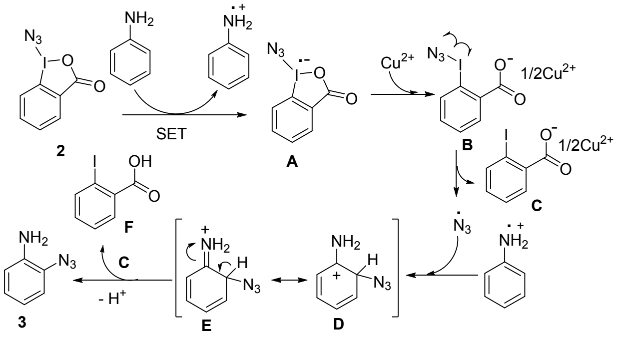

Scheme 2 Plausible mechanistic pathways.

Notes and references

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