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Copper-catalysed regioselective azidation of arenes by C-H activation directed by pyridine

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Chandra S. Azad[a] and Anudeep K. Narula[a]*

A novel and efficient copper-catalysed pyridine directed ortho-azidation of arenes has been developed using safe and stable benzotriazole sulphonyl azide as azidating agent. A variety of organo azides have been synthesized having electron donor and withdrawing group, thereby the azide products can be easily transformed into assorted functionalities.

Organic azides have been identified as important compounds and are extensively used in organic synthesis as intermediate or as "masked amine".[1] One of the major utilities of azides are in the "click chemistry".[2] The cyclo- adduct products of azides have been explored in all aspects of drug discovery, ranging from lead discovery to proteomics and DNA research using bio-conjugation reaction.[3] In addition to their important role in click chemistry, aromatic azides are known for providing an electro-deficient nitrene species, which are able to show insertion reaction into a C-H bond.[4] The azide pro-drugs of corresponding amine are often better able to cross the blood-brain barrier (BBB) than the corresponding drugs by avoiding enzymatic deamination. The successful examples reported so far are azide derivatives of cordycepine, 2'-F-ara-ddll, vidarabine, acyclovir, penciclovir and other related drugs.[5] Therefore, the introduction of an azide group into organic framework are of great importance and interest.[6]

Literature survey showed that, several methodologies are available for the synthesis of aliphatic azides, although methodologies for the synthesis of aryl azides are still very few. The five classical main methodologies for the synthesis of aryl azides are (i) nucleophilic aromatic substitution (S_NAr) of activated aryl azide, sulphonates, nitro groups and boronic acid (ii) diazotisation of aromatic amine, (iii) reaction of Grignard or lithium reagent with tosylazide, (iv) reaction of aryl amines with azide transfer reagent and (v) N-nitrosation reaction of aromatic hydrazines, using nitrosation reagent.[7] Even though these reactions are of good synthetic utility, they suffer from a prolonged reaction time, harsh reaction conditions, use of additives, which interfere with the other functionality present on the substrate.

Transition metal catalyzed direct activation /functionalization of C-H bond is one of the main emerging strategies that is currently attracting remarkable effort with the challenge to afford alternative environmental friendly and efficient ways for the construction of C-N bond.[8] Therefore it is attractive to take advantage of pervasiveness of C-H bond activation/functionalization for making it much more ideal, straight forward and step economic azidation process.[9] The C-H azidation reaction is generally accomplished in the presence of hypervalent iodine because of less acidity and high strength of C-H bond.[10] Kita and Suna used the hypervalent iodine reagents $PhI(TFA)_2$ and $PhI(OAc)_2$ respectively for electrophilic azidation.[11] Jiao and Tang reported copper catalyzed, amine directed ortho-azidation of aniline.[12] Hao and co-worker developed the oxidant free copper(II) catalyzed methodology for ortho-azidation of aniline using azido-benziodoxolone.[6a] Punniyamurthy and his group reported the elegant synthesis of benzimidazole in which aniline schiff's base regioselectively azidated with copper(I) and $TMSN_3$.[13] However, the hazardous and toxic azide source, such as NaN_3, $TMSN_3$, still used in these reactions are restricting their synthetic utility.

Recently, the transition metal assisted using 2-pyridyl as a directing group have received considerable attention, and presently arenes can be functionalize regioselectively by diverse groups by this method.[14] Wang and coworkers excellently explored the scope of Cu catalyzed, chelation assisted C-H activation on azacalix[1]arenes[3]pyridine.[15] Literature survey showed, only one procedure, reported by X Li, described Rh (III) catalyzed efficient mono ortho C-H azidation of 2-phenyl pyridine.[16] Unfortunately, this method has limited utility because of use of the expensive catalyst and hazardous and toxic NaN_3. In continuum of developing copper catalyzed novel synthetic methods for the synthesis of biologically important scaffolds,[17] herein the first copper catalyzed regioselective direct ortho C-H azidation of 2-phenyl pyridine using benzotriazole sulphonyl azide ($BtSO_2N_3$) as azide source, 1,2,3-trichloropropane (TCP) as solvent and potassium persufate ($K_2S_2O_8$) as terminal oxidant is reported. One of the

[a] "Hygeia"Centre of Excellence in Pharmaceutical Sciences (CEPS), GGS Indraprastha Univeristy, Sec. 16-C, Dwarka, New Delhi, 110078 (India) Email: medchemlab58@gmail.com

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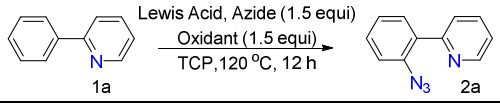
novel finding is the use of imidazole sulphonyl azide ($ImSO_2N_3$) hydrochloride and benzotriazole sulphonyl azide ($BtSO_2N_3$) as azide source. These organic azide transfer reagents are relatively stable and safe to handle with a long shelf-life, good solubility in most of the organic and aqueous solvents, which motivated us to use these regents as azide source.[18] This manuscript represent a new approach to cost-effective regioselective aromatic azidation directed by pyridine.

Primarily, a review on reaction parameters, including catalyst, azide source, oxidant and solvent, was conducted at fixed temperature of 120° C and reaction time 12 h using the azidation of 2-phenylpyridine (**1a**) as a model substrate. The reported methods from Hao , Wang and Zhu reinvigorated us to use copper as a catalyst in the reaction medium and polar solvent as a reaction medium.[6a,15,19] After concernig the importance of haloginated solvents in C-H bond activation, high boiling TCP was solvent of choice.[19a,20] Firstly catalyst (CuI) loading was studied from 0.75 mol % to 10 mol % and satisfying yield was observed when 5 mol % catalyst was used, excess catalyst did not have profound effect on the yield (Table **1**, entries **1**-**5**). In order to find the better catalyst, other copper salts were also screened. The copper bromide and copper chloride led to the formation of **2a** in 52 and 44% yield respectively, with the recovery of substrate **1a** (Table **1**, entries **6** and **7**). It is interesting to note that $Cu(OAc)_2$ led to the formation of desired product in 62 % yield and Cu(OAc) gave 72% yield, although it required longer reaction time (24 h) and higher temp 140°C (Table 1 entries **8** and **9**). Other copper salts used were found to be less effective in term of effective conversion, Cu_2O gave only 12 % yield and found to be least effective (Table **1**, entries **10**-**12**). Furthermore, considering the importance of palladium in C-H bond activation, some easily accessible Pd salts were examined for the purpose. It was found that $Pd(OAc)_2$ and $PdCl_2$ led to formation of **2a** in 34 and 23 % respectively (Table **1** entries **13**- **14**) . The $Pd(OH)_2$/C was found to be ineffective as it gave traces of product with recovery of starting material after 24 h heating at 140°C(Table **1** entry **15**). After confirming the importance and stoichiometry (5 mol %) of CuI, the oxidants were screened in which potassium persulphate $K_2S_2O_8$ displayed superior results in 1.5 equivalnet stoichiometry, while $(NH_4)_2S_2O_8$, air, TBHP, $Hgb\text{-}H_2O_2$, Oxone and H_2O_2 afford the target molecule in <67% yield (Table **1** entries **16**-**21**). Afterward the azide source was screened, NaN_3 and $ImSO_2N_3$.HCl found to be effective in yielding product in 75 and 78% respectively, while $TMSN_3$, TfN_3 and TSN_3 gave the targeted molecule in <66% yield (Table **1** entries **22**-**26**). The higher yield in case of $BtSO_2N_3$ may be due to excellent solubility of azide donor in TCP. The high stoichiometric ratio of azide source can be explained on the basis of stability of $BtSO_2N_3$, as loss of mass is evidanced at high temperature in Thermogravimetric (TGA) analysis.[18a] Control experiment ascertained that, without the catalyst and oxidant, the product was not formed (Table **1** entries **27**-**28**).

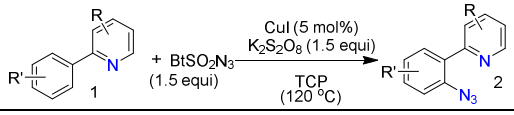
Table 1. Optimisation of reaction condition[a]



Entry	Catalyst (mol%)	Oxidant (1.5 equi)	Azide (1.5 equi)	Yield[b]
1	CuI (0.75)	$K_2S_2O_8$	$BtSO_2N_3$	14
2	CuI (1.5)	$K_2S_2O_8$	$BtSO_2N_3$	43
3	CuI (3)	$K_2S_2O_8$	$BtSO_2N_3$	76
4	**CuI (5)**	$K_2S_2O_8$	**$BtSO_2N_3$**	**92**
5	CuI (10)	$K_2S_2O_8$	$BtSO_2N_3$	91
6	CuBr (5)	$K_2S_2O_8$	$BtSO_2N_3$	52
7	CuCl (5)	$K_2S_2O_8$	$BtSO_2N_3$	44
8	$Cu(OAc)_2$ (5)	$K_2S_2O_8$	$BtSO_2N_3$	62
9	CuOAc (5)	$K_2S_2O_8$	$BtSO_2N_3$	72[c]
10	$Cu(OTf)_2$	$K_2S_2O_8$	$BtSO_2N_3$	56
11	CuF_2	$K_2S_2O_8$	$BtSO_2N_3$	35
12	Cu_2O	$K_2S_2O_8$	$BtSO_2N_3$	12
13	$Pd(OAc)_2$	$K_2S_2O_8$	$BtSO_2N_3$	34
14	$PdCl_2$	$K_2S_2O_8$	$BtSO_2N_3$	23
15	$Pd(OH)_2$/C	$K_2S_2O_8$	$BtSO_2N_3$	trace[d]
16	CuI	$(NH_4)_2S_2O_8$	$BtSO_2N_3$	52
17	CuI	air	$BtSO_2N_3$	trace[d]
18	CuI	TBHP	$BtSO_2N_3$	66
19	CuI	$Hgb\text{-}H_2O_2$	$BtSO_2N_3$	46
20	CuI	Oxone	$BtSO_2N_3$	67
21	CuI	H_2O_2	$BtSO_2N_3$	Trace[c,d]
22	CuI	$K_2S_2O_8$	$ImSO_2N_3$	78
23	CuI	$K_2S_2O_8$	$TMSN_3$	62
24	CuI	$K_2S_2O_8$	NaN_3	75
25	CuI	$K_2S_2O_8$	TfN_3	66
26	CuI	$K_2S_2O_8$	TsN_3	24
27	None	$K_2S_2O_8$	$BtSO_2N_3$	---
28	CuI	None	$BtSO_2N_3$	---

[a] Reagent 1 (1mmol and 5 ml/mmol TCP), catalyst other than CuI screened at 5 mol% scale. [b]Isolated yield. [c] Reaction completed in 24 h at 140°C.[d] Trace amount was spotted on TLC.

Table 2. Synthesis of 2-azidoaromatics.[a]



Entry	R'	R	Time (h)	2	Yield (%)[b]
1.	H	H	12	2a	92
2.	H	4-Me	14	2b	84
3.	H	5-Cl	12	2c	83
4.	H	5-Me	15	2d	79
5.	2-OBn	H	16	2e	81
6.	2-Me	H	12	2f	90
7.	2-Cl	H	15	2g	86
8.	4-Me	H	16	2h	82
9.	4-OMe	H	12	2i	76
10.	4-CN	H	14	2j	56
11.	4-CHO	H	24	2k	52[c]
12.	4-CO_2Me	H	24	2l	52

13.	2,5-diMe	H	22	2m	32
14.	——— [d]	H	18	2n	75
15.	——— [e]	H	15	2o	81
16.	3-Br	H	12	2p	82

[a] Reaction condition: 1 (1equivalent), CuI (5 mol%) , $BtSO_2N_3$ (1.5 equivalent), $K_2S_2O_8$ (1.5 equivalent) in TCP (5 mL/mmol). [b] Isolated yield. [c] oxidation of aldehyde occurred as identified by TLC and NMR analysis, and beside 2k the oxidised product (un-azidated) was also isolated by column chromatography in minor quantity. [d]2-thienyl. [e]2-naphthalenyl

With the optimised relation condition in hand, the substrate scope and limitation of the reaction was examined in the presence of 5 mol % of the copper catalyst and the result are summarised in table **2**. 2-Phenylpyridines bearing electron-donating and halogen group in the pyridine ring were well endured in the reaction conditions, and the azidation products **2a**-**2d** were isolated in good to excellent yield (table **2** entries **1**-**4**). Likewise, smooth and clean reaction was observed for 2-Phenylpyridines having electron-donating, electron withdrawing, and halogen group at the different position of phenyl ring (Table **2** entries **5**-**9**), though substrate with electron withdrawing group gave the lesser yield, (Table **2** entries **10**-**12**). The functional group present on the substrate provide suitable site for further functionalization. Additionally, the efficiency of the reaction was confirmed by the successful azidation of di-substituted, fused and heterocyclic ring system (Table **2** entries **13**-**15**). The longer reaction time and low yield are in agreement of steric hindrance caused by di-substitution. In the case of unsymmetrical *m*-Bromo substrate azidation occurred exclusively at the least hindered position (table **2** entry **16**).

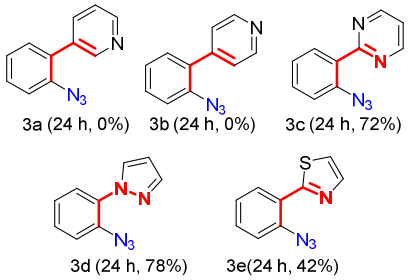
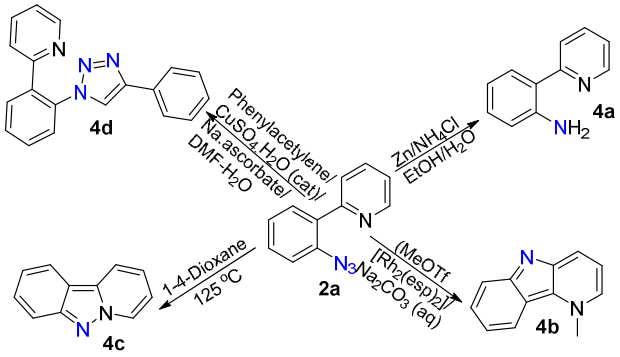


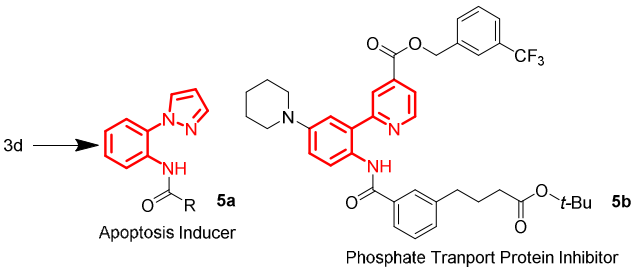
Figure 1. C-H bond azidation of arenes with different directing Group.

Undoubtedly, a suitable directing group was essential to obtain both high yield and high efficacy for *ortho*-C-H azidation of arenes. The chelating group appeared to be important for the ortho C-H azidation of arenes because no reaction was observed for 3- and 4-phenylpyridine (Figure **1**, **3a** and **3b**). Other common directing groups, including pyrimidine, pyrazole and thiazole, could be similarly active to direct ortho C-H azidation, nevertheless relative lower yield and longer reaction times are expected as comparison to 2-phenylpyridines (Figure **1**, **3c**-**e**). In all cases, no di azidation product was formed. Yu and co-worker got the di substitution as of highly activating nature of aniline, on the other hand in our substrate no such activation is observed as direction is achieved by pyridine.[21]



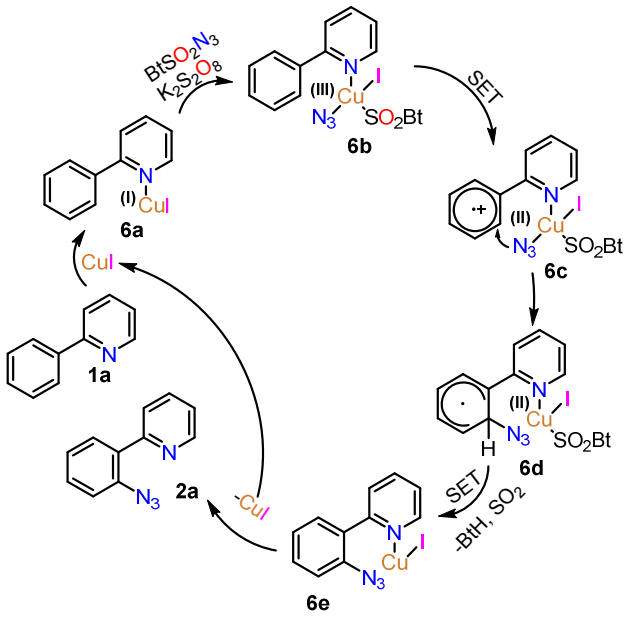
Scheme 1. Functionalization of ortho-azide arenes

The synthetic usefulness of azidation product was further demonstrated by three additional reaction (Scheme 1). As represented in scheme **1**, reduction of azide (**2a**) achieved by treatment with Zn and NH_4Cl in reflux EtOH, providing 92% yield of amino derivative **4a**.[22] The reduced amine products of ortho-N-heterocyclic are useful starting material in the synthesis of bi-dentate nitrogen ligands, *e.g.* N-tosyl derivative of **4a** was an effective bi-dentate ligand for fluorination.[23] Recently, Driver and co-workers reported the conversion of **2a** into carboline **4b** by using $[Rh_2(esp)_2]$ as a catalyst.[24] α-carbolines are known as antiviral agents, inhibitors of ApoB-100-associated lipoprotein production for cholesterol lowering, and more recently, as inhibitors of CDK1 kinase as potential anticancer agents.[25] The **2a** was successfully converted into pyrido[1,2-b]indazole (**4c**) by heating at 125° C in 1,4-Dioxane.[16] Pyrido[1,2-b]indazole core is well described as tubulin binding anticancer agents.[26] A click reaction of **2a** and phenylacetylene afford triazole **4d** in 81% yield, which could be used as a precursor to N-hetrocyclic carbene ligand.[27] Moreover **5a** which is known to be an apoptosis inducer can be synthesize using developed methodology using **3d** as a starting material.[28] The active core of compound **5b** (PTP Inhibitor) can be synthesize by developed methodology (Scheme 2).[29]



Scheme 2. Application of methodology in phamaceutical chemistry.

On the basis of reported investigations and our results, the reaction mechanism was hypothesised.[6a,16,30] Initially, the reaction is performed using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as radical scavengers, and it was found that azidation reaction was completely inhibited, suggesting radical mechanism pathway So it is postulated that, firstly 2-phenylpyridine was co-ordinated to copper iodide to form **6a**, which on reaction with $BtSO_2N_3$ converted into Cu(III) possessing SO_2Bt, N_3 and iodine in presence of $K_2S_2O_8$ as oxidant (**6b**). The iodide might be responsible for stabilising the variation in oxidation state of Cu as iodine itself showed variable oxidation states. The **6b** converted into radical cation **6c** by single electron transfer (SET) in which intramolecular azide transfer takes place to form **6d** radical. Another SET resulting the formation of **6e** with the elimination of benzotriazole and SO_2 which furnish the target product **2a**, with completion of catalytic cycle (Scheme **3**).



Scheme 3. Plausible reaction mechanism.

In continuity of finding the accessibility of the reaction on wide range of substrate, the ortho-CH activation of aniline by developed methodology was investigated, unfortunately no satisfactory results were obtained as yield was very low. In "Hygeia" the optimisation of this methodology for ortho-CH activation of aniline are in progress and successful result will be reported very soon.

Conclusions

In conclusion, authors developed a novel copper catalysed ortho C-H bond azidation of arenes with safer and stable $BtSO_2N_3$ using $K_2S_2O_8$ as a terminal oxidant and TCP as solvent, synthesis of azidoarenes with excellent regioselectivity and yield. The efficient ortho-directing effect of pyridine, was ascertained with number of substrate and SET mediated mechanism proposed for the reaction. This innovative cost effective, safe, and operative finding provided as easy access for additional chemical modifications of the 2-(2-azidophenyl)pyridine derivatives.

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Copper-catalysed regioselective azidation of arenes by C-H activation directed by pyridine

Chandra S. Azad and Anudeep K. Narula*