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Copper-Mediated Regioselective Efficient Direct *ortho*-Nitration of Anilide Derivatives

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The mild and readily available $Cu(NO_3)_2$ mediated *ortho* nitration of anilides with broad substrate using $K_2S_2O_8$ as an oxidant in the absence of any other metal catalyst and nitrating agent under mild conditions was reported for the first time.

Keywords: Regioselective *ortho* nitration Cheap and readily available nitrating source Mild reaction conditions Broad substrate scope

Because the nitro group is a primary precursor of amines and show its unique responsibility in various industrial, material and pharamcological applications, its installation into organic small molecules has always been a rousing attention to synthetic and research commune.¹ However, the classical electrophilic nitration of arenes is well known method for the nitro group incorporation till date, several considerable limitations including excessive acid waste, low yield, site selectivity. intolerance of various organic functionalities, over nitration and over oxidation were always anticipated the chemist for developing suitable alternative approaches.² Hence, for the past few decades a plethora of transition metal catalyzed nitration methods namely ipso-nitration of aryl boronicacids, aryl carboxylic acids, aryl halides, pseudohalides, and organometallics etc., were developed.³ Among them, the transition metal catalyzed directing group assisted regioselective C(Ar)-H bond to C(Ar)-NO₂ was considered as relatively better and convenient approach,

it is atom and step economy, mild,

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environmentally benign and operationally simple. In view of the importance of ortho-Nitroprecursors for the construction of anilides pharmacologically active 2-substituted indoline and Benzimidazole derivatives and the significance of aryl sulfonamides as cheap nitrogen sources with huge availability,⁴ few Cu, Ag, Fe and Pd-catalyzed direct regioselective nitration of anilides and sulfonamides were reported in the literature.^{4d, 5} Despite the advances, these protocols associated with few shortcomings which include both the necessity of metal catalysts & external nitrating agents, longer reaction times and typical reaction conditions.

Due to the exclusive parameters including flexible reactivity, little toxicity, inexpensiveness, easy accessibility, operationally simplicity and eco-friendly nature, copper nitrate has gain a special place in synthetic organic chemistry.⁶ Consequently, the copper and oxidant for several organic transformations. 5a, 7

Moreover, the precise use of copper nitrate as an efficient nitrating source in the regioslective C(Ar)–H bond nitration of indoline and BN-arenes phenols and electron rich arene compounds ⁸⁻¹² in the absence of metal catalyst was also reported.¹³ Encouraged by all these reports and keeping the importance of anilides and sulphonamides in mind, we herein describe the use of copper nitrate reagent in the efficient regioselective *ortho*-nitration of several anilides and sulfonamides using $K_2S_2O_8$ without the need of any metal catalyst under mild conditions.

To set the optimal reaction conditions for the regioseletive nitration, we have chosen N-phenyl benzamide 1a as a model substrate. After the investigation of several reaction parameters, the standard conditions for the present nitration approach were established and the results were clearly depicted in table 1. We achieved the good yield (79%) of desired *ortho*-nitro-*N*-phenyl benzamide (2a) using 1.1 equivalents of Cu(NO₃)₂.3H₂O as a nitro source, 1.5 equivalents of K₂S₂O₈ as an oxidant in MeCN at 80 °C (Table 1, entry 2). The reaction was unsuccessful in the absence of any oxidant (Table 1, entry 1). The use of other oxidants like PhI(OAc)₂, Benzoyl Peroxide, tert-Butyl hydroperoxide (TBHP), Di-tert-butyl peroxide (DTBP), oxone and O_2 were also not much influential on the yield of 2a, as compared to K₂S₂O₈ (Table 1, entries 3-8). We then screened the efficacy of other nitrating agents and to our surprise no products was obtained with NaNO₃ (Table 1, entry 9) and KNO₃ (Table 1, entry 10). On the other hand 54% yield of desired product 2a was achieved using $Fe(NO_3)_2 \cdot 9H_2O$ (Table 1, entry 11). Furthermore, the use of $Ni(NO_3)_2$ and Zn(NO₃)₂ has provided the 31% and 26% yield of 2a correspondingly (Table 1, entries 12 and 13). Of the various solvents screened, solvents such as DMSO, DMF, toluene, AcOH, EtOH and H₂O were ineffective in the present protocol (Table 1, entries 14-19), whereas the DCE has provided the 55% yield of 2a (Table 1, entry 20). Varying the stoichiometric amount of Cu(NO₃)₂ and K₂S₂O₈ from 1.0 and 1.5 equivalents respectively, did not increase the yields of the product 2a (Table 1, entries 21-23), Further, changing the reaction temperature from 80 °C has also led to decrease the yield of desired product 2a (Table 1, entries 24-25). The reaction yield was not affected by the N_2 atmosphere (Table 1, entries 26).



Entry	M (NO ₃) ₁₋₃	Oxidant	Solvent	%Yield ^b
	(equiv.)			
1	$Cu(NO_3)_2 \cdot 3H_2O$	-	ACN	00
2	$Cu(NO_3)_2 \cdot 3H_2O$	$K_2S_2O_8$	ACN	79
3	$Cu(NO_3)_2 \cdot 3H_2O$	PhI(OAc	ACN	00
)2		
4	$Cu(NO_3)_2 \cdot 3H_2O$	Benzoyl	ACN	00
-		Peroxide		00
3	$Cu(NO_3)_2 \cdot 3H_2O$	ТВНР	ACN	00
6	$Cu(NO_3)_2 \cdot 3H_2O$	DTBP	ACN	00
7	$Cu(NO_3)_2 \cdot 3H_2O$	Oxone	ACN	49
8	$Cu(NO_3)_2 \cdot 3H_2O$	O ₂	ACN	00
9	Na(NO ₃)	$K_2S_2O_8$	ACN	00
10	K(NO ₃)	$K_2S_2O_8$	ACN	-
11	Fe(NO ₃) ₃ ·9H ₂ O	$K_2S_2O_8$	ACN	54
12	$Ni(NO_3)_2 \cdot 6H_2O$	$K_2S_2O_8$	ACN	31
13	$Zn(NO_3)_2 \cdot 3H_2O$	$K_2S_2O_8$	ACN	26
14	$Cu(NO_3)_2 \cdot 3H_2O$	$K_2S_2O_8$	DMSO	-
15	$Cu(NO_3)_2 \cdot 3H_2O$	$K_2S_2O_8$	DMF	-
16	$Cu(NO_3)_2 \cdot 3H_2O$	$K_2S_2O_8$	Toluene	-
17	$Cu(NO_3)_2 \cdot 3H_2O$	$K_2S_2O_8$	AcOH	-
18	$Cu(NO_3)_2 \cdot 3H_2O$	$K_2S_2O_8$	EtOH	-
19	$Cu(NO_3)_2 \cdot 3H_2O$	$K_2S_2O_8$	H ₂ O	-
20	$Cu(NO_3)_2 \cdot 3H_2O$	$K_2S_2O_8$	1, 2-DCE	55
21°	$Cu(NO_3)_2 \cdot 3H_2O$	$K_2S_2O_8$	ACN	21
22 ^d	$Cu(NO_3)_2 \cdot 3H_2O$	$K_2S_2O_8$	ACN	46
23e	$Cu(NO_3)_2 \cdot 3H_2O$	$K_2S_2O_8$	ACN	76
24 ^f	$Cu(NO_3)_2 \cdot 3H_2O$	$K_2S_2O_8$	ACN	17
25 ^g	$Cu(NO_3)_2 \cdot 3H_2O$	$K_2S_2O_8$	ACN	61
26 ^h	$Cu(NO_3)_2 \cdot 3H_2O$	$\overline{K_2S_2O_8}$	ACN	77

^a Reaction was performed: **1a** (1.0 mmol, Cu(NO₃)₂·3H₂O (1.0 equiv), $K_2S_2O_8$ (1.5 equiv) and ACN (5.0 mL) at 80 °C, in open air. ^bIsolated yield. ^c Cu(NO₃)₂·3H₂O (0.5 equiv), ^d $K_2S_2O_8$ (1.0 equiv), ^e $K_2S_2O_8$ (2.0 equiv), ^f 40 °C and ^g 60 °C, ^h N₂ atm.

With the optimized conditions in hand, the substrate scope of this reaction was investigated (Table 2). The results showed that a wide range of anilides and sulfonamides reacted smoothly under standard reaction conditions to produce the corresponding nitrated products (2a-2q). Excellent yields were achieved with the electron donating alkyl and alkoxy groups such as methyl 93%, ethyl 92%, methoxy 95% in para position of the aniline ring (Table 2, 2b-2d), whereas, the *ortho* methylated substrate has decreased the yield of corresponding product to 45% (Table 2, 2e). Substrate

2f in 88% yield. The Moderate yields were achieved in the case of halogen substituents such as, 4-fluoro, 4-Iodo and 4-trifluoro methyl groups present on the para position of aniline ring (Table 2, **2g-2i**). Under the standard reaction conditions, strong electron withdrawing group 4-Nitro failed to produce the desired product (Table 2, **2j**).

 Table 2. Substrate scope of regioselective nitration of anilide and sulfonamides.^{a,b}



^aReaction was performed: **1** (1.0 mmol, Cu(NO₃)₂·3H₂O (1.0 equiv), $K_2S_2O_8$ (1.5 equiv) and ACN (5.0 mL) at 80 °C, in open air, ^b Isolated yield.

The para- methyl and trifluromethyl benzamide substrates afforded the desired products in 82% and 71% yields respectively (Table 2, 2k, 2l). Further, the anilide substrates consist of alkyl and pyrdiyl group are produced the corresponding products in the range of 83-89% yields (Table 2, 2m-2o). Furthermore, aryl sulfonamides were found to compatible, to give corresponding products in 76% and 71% respectively (Table 2, 2p-2q).

To study the further electronic effect on the rate of the reaction, we conducted intermolecular competition experiments between an electron-neutral and electron-rich/deficient, substrates under the standard were preferentially functionalized, and electron-neutral substrate produced a mixture of products (Scheme 1, Equation 1). The high level of chemoselectivity is showed by performing competition experiment between N-phenylbenzamide and N,N-dimethylaniline, N,Ndimethylaniline was resistant to nitration while the Nphenylbenzamide was produced desired product **2a** 60% yields (Scheme 1, Equation 2). The amide proton of N-phenylbenzamide was subistituted with methyl group (**1r**) inhibits the ortho-nitration of Nphenylbenzamide **2r** (Scheme 1, Equation 3.) **Scheme 1: Competition experiments.**

Scheme 1: Competition experiments.



To gain insight into the region-selective nitration protocol, radical trapping experiments were performed. Reaction in the presence of radical scavengers such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), Butylated hydroxytoluene (BHT) and 1,1-Diphenylethylene (1,1 DPE) the reactions were yielded in trace amounts 7-13% of desired product, under standard reaction condition (Scheme 2).^{5a} These experiments demonstrate that the regioselective nitration protocol may proceed by radical mechanisms with the existence of a nitro radical. On the other hand, N-substitution (Scheme 1) may prevent the formation of an anilide radical intermediate upon the one-electron oxidation by the Cu⁺² species.¹⁴





Based on these results and literature reports, ^{4d, 5a, 14} we proposed the plausible reaction mechanisms of

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Scheme 3. First, assumed that the initial one-electron oxidation of the anilide by copper(II) results in the formation of anilide radical intermediate. Subsequently, this intermediate undergoes a reversible transformation followed by the attack of the NO_2 radical at the *ortho*-position of aniline ring to produce the corresponding nitration product.

Scheme 3: A plausible mechanistic pathway.



In conclusion, we have developed a simple and efficient copper mediated regioselective nitration of anilides and sulfonamides has been established using an inexpensive and commercially available copper reagent and potassium persulfate under mild conditions. A series of nitrated anilides and sulfonamides derivatives were achieved in good to moderate yields.

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A Supplementary data

Experimental details, characterization data and copies of ¹H and ¹³C NMR spectrum of products can be found, in the online version at http://dx.doi.org/

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Declaration of interests

 \boxtimes The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

□The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Graphical Abstract:

The mild and readily available $Cu(NO_3)_2$ mediated *ortho* nitration of anilides with broad substrate using $K_2S_2O_8$ as an oxidant in the absence of any other metal catalyst and nitrating agent under mild conditions was reported for the first time.



Highlights:

- Regioselective ortho nitration
- Cheap and readily available nitrating source.
- Mild reaction conditions
- ✤ Broad substrate scope.