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New method for the preparation of *N*-chloroamines by oxidative *N*-halogenation of amines using oxone-KCl

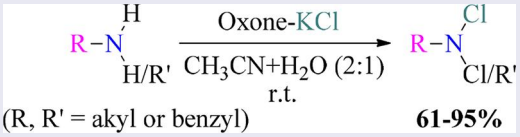
Vinodkumar Sriramoju, Srinivas Kurva, and Sridhar Madabhushi

Fluoroorganics Division, CSIR-Indian Institute of Chemical Technology, Hyderabad, India

ABSTRACT

A mild and efficient method for preparation of *N*-chloroamines by oxidative *N*-halogenation of primary/secondary amines using oxone-KCl is described.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
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KEYWORDS
Amines; *N*-chloroamines; oxidative *N*-halogenation; oxone-KCl

Introduction

N-chloroamines are important intermediates in organic synthesis for preparation of nitriles,[1] chloroimines,[1a] diazirines,[2] diazene *N*-oxides,[3] aroyliminoselenyl-chlorides,[4] nitramides[5] and aminoketones.[6] *N*-chloroamines are also studied as cross-coupling partners for Buchwald-Hartwig type electrophilic amination reactions.[7,8] In literature, several methods were known for preparation of *N*-chloroamines by oxidative *N*-halogenation using reagents such as *m*-chloroperbenzoic acid-$FeCl_3$,[1a] isocyanuric chloride,[1b] *N,N,N′,N′*-tetrachlorobenzene-1,3-disulfonamide,[1c] $Ca(OCl)_2$,[1d] Cl_2-H_2O,[6] *N*-chlorosuccinimide (NCS)[9] and *t*-BuOCl.[10]

Oxone is a mild, inexpensive solid oxidant and widely used in organic synthesis. Oxone efficiently promotes oxidative halogenation reactions in the presence of a halide source in aqueous organic medium such as acetonitrile–water, acetone–water, methanol–water, etc. Some of the important oxidative halogenation reactions reported in literature using oxone-MX system are (i) nuclear chlorination of aromatic compounds,[11] (ii) transformation of alkynes into α,α-dihaloketones,[12] (iii) alkynyl silanes into α,α,α-trihaloketones,[13] (iv) thiols into sulfonyl halides[14] (iv) alkenes into halohydrins,[15] (v) oximes into hydroximoyl chlorides[16] etc.

In literature, studies on transformation of amines into *N*-chloroamines by reaction with oxone and a halide are so far not known. Here, we report for the first time, a mild and efficient method for preparation of *N*-chloroamines in high yields (61–95%) from a variety

CONTACT Sridhar Madabhushi smiict@gmail.com Fluoroorganics Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India.
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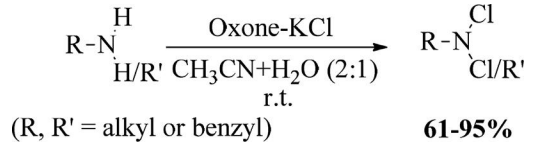


Scheme 1. Synthesis of *N*-chloroamines using oxone-KCl.

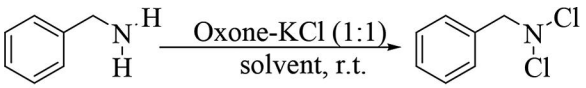
of primary and secondary amines by oxidative *N*-halogenation using oxone-KCl at ambient temperature in acetonitrile-water (2:1) as shown in Scheme 1.

In this study, initially we found that benzylamine **1a** reacts efficiently with oxone-KCl in aqueous acetonitrile at ambient temperature producing *N,N*-dichlorobenzylamine **2a**, which was obtained **2a** in maximum yield (95%) when **1a** was reacted with two equivalents of oxone-KCl in acetonitrile–water (2:1) medium as shown in Table 1.

Next, we found that the present reaction proceeds well also with a variety of primary aralkyl amines **1a–1k**, alkyl amines **1l–1o** and secondary alkyl amines **1p–1r**, which were reacted with oxone-KCl in acetonitrile–water (2:1) medium at ambient temperature to obtain the corresponding *N,N*-dichloroamines **2a–2o** in 61–95% yields and *N*-chloroamines **2p–2r** in 84–88% yields.

In literature, it is reported that activated arenes such as anisoles and phenols undergo regioselective ring chlorination with oxone-KCl in acetonitrile.[11a] In the present study, when aralkyl amines **1a–1k**, which have electron releasing and electron withdrawing groups on the aromatic ring, were reacted with oxone-KCl in aqueous acetonitrile, aralkyl amines **1a–1i** were found to produce exclusively *N*-chlorinated products **2a–2i** in 85–95% yields. However, under similar reaction conditions, 3-methoxybenzylamine **1j** and 4-methoxybenzylamine **1k** behaved differently as they underwent simultaneously ring chlorination as well as *N*-chlorination producing *N,N*-dichloro-1-(2-chloro-5-methoxyphenyl)methanamine **2j** and *N,N*-dichloro-1-(3-chloro-4-methoxyphenyl)methanamine **2k** in 63 and 61% yields respectively (Table 2). Here, it appears that oxidative *N*-chlorination proceeds possibly through radical reaction pathway involving chlorine radicals (Cl·), which are generated by the homolytic fission of the *in situ* generated hypochlorous acid (HOCl) and ring chlorination proceeds through electrophilic chlorination pathway by reaction of

Table 1. Screening of solvents for *N*-chlorination of benzylamine **1a** using oxone-KCl.

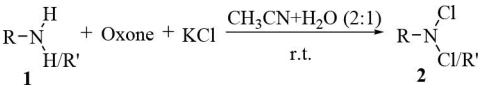


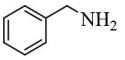
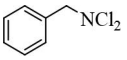
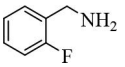
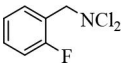
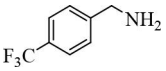
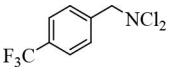
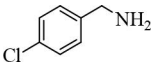
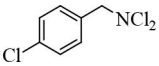
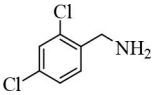
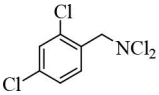
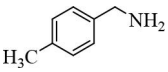
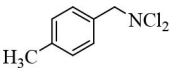
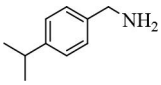
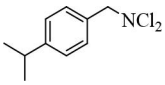
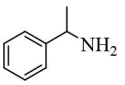
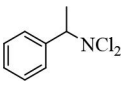
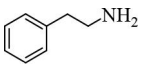
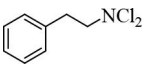
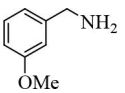
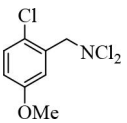
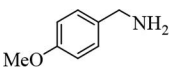
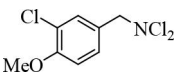
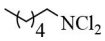
1a **2a**

Entry	Oxone (equi)	KCl (equi)	Solvent	Reaction time (min)	%Yield[a]
1	1	1	$CH_3CN + H_2O$ (2:1)	25	48
2	1.5	1.5	$CH_3CN + H_2O$ (2:1)	25	60
3	2	2	$CH_3CN + H_2O$ (2:1)	25	95
4	2	2	$CH_3CN + H_2O$ (2:1)	60	40
5	2	2	$CH_3CN + H_2O$ (2:1)	60	30
6	2	2	CH_3CN	60	15
7	2	2	$CHCl_3$	60	10
8	2	2	THF	60	10

[a]Isolated yields.

Table 2. *N*-chlorination of various primary and secondary amines.



Entry	Amine 1	*N*-chloroamine 2	Time (min)	%Yield[a]
a			25	95
b			40	85
c			40	85
d			25	86
e			35	89
f			30	90
g			40	88
h			20	87
i			30	91
j			30	63
k			30	61
l			25	90
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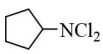
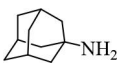
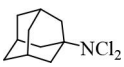
n			30	87
o			45	84
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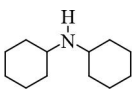
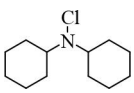
q			45	84

(*Continued*)

Table 2. Continued.

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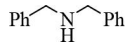
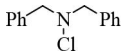
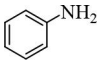
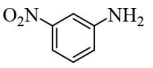
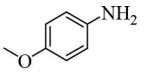
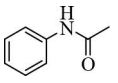
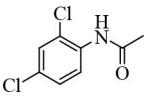
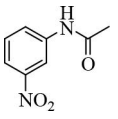
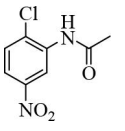
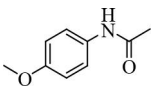
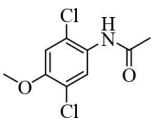
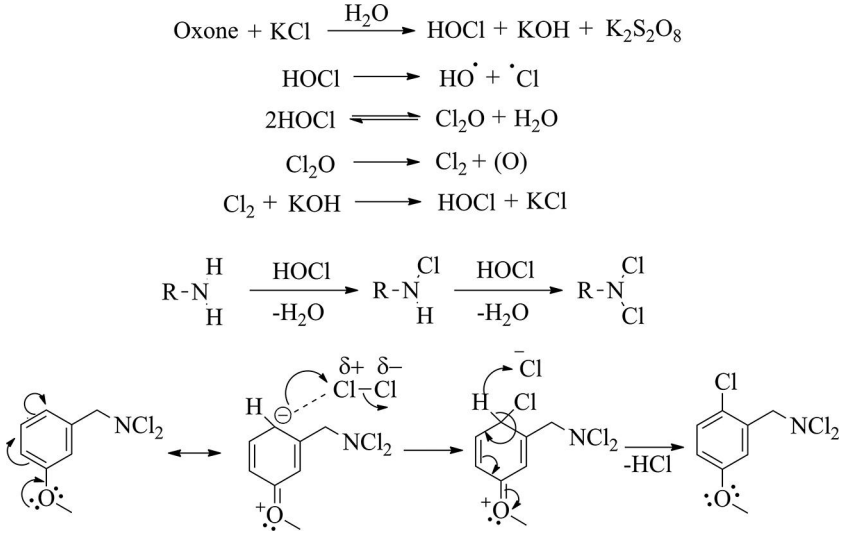
r			20	85
s		–	60	NR
t		–	60	NR
u		–	60	NR
v			30	65
w			35	45
x			25	51

[a]Isolated yields.
All products gave satisfactory ^{1}H & ^{13}C NMR, IR and mass spectral data.
NR, no reaction.

in situ generated chlorine with an activated arene such as methoxylated benzene as shown in Scheme 2. Though chlorine is not a good electrophile, substrates **1j** and **1k** showed remarkable reactivity and underwent electrophilic ring chlorination with chlorine. It could



Scheme 2. Plausible mechanism for *N*-chlorination and ring chlorination reactions.

be due to the presence of high activating methoxy functionality on the aromatic rings of these substrates.[17]

In our study, aryl amines such as aniline **1s**, 3-nitroaniline **1t** and 4-methoxyaniline **1u** were found to be unreactive with oxone-KCl under the reaction conditions. However, their acetanilide derivatives, i.e., **1v–1x** were found to be reactive under similar conditions and formed exclusively ring chlorination products,[11a] i.e., *N*-(2,4-dichlorophenyl)acetamide **2v**, *N*-(2-chloro-5-nitrophenyl)acetamide **2w** and *N*-(2,5-dichloro-4-methoxyphenyl)-acetamide **2x** in 65, 45, and 51% yields respectively.

Conclusion

In conclusion, this work describes an efficient method for preparation of *N*-chloroamines from a variety of primary and secondary amines by oxidative *N*-chlorination under mild conditions using oxone-KCl.

Experimental section

Typical procedure for the synthesis of N,N-dichlorobenzylamine (2a): In a 50 mL round bottom flask, benzylamine **1a** (0.5 g, 4.67 mmol), oxone (2.9 g, 9.35 mmol), NaCl (0.55 g, 9.35 mmol) and acetonitrile-water (2:1, 10 mL) were taken and stirred at room temperature for 25 min. After completion of the reaction (TLC), the reaction mixture was extracted with ethyl acetate (3 × 10 mL) and the combined organic layer was washed with brine (1 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by normal column chromatography (silica gel 60–120 mesh, *n*-hexane) furnished *N,N*-dichlorobenzylamine **2a** as yellow liquid (0.78 g, 95%). The characterization data obtained for **2a** is as follows: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.39–7.36$ (m, 5H), 4.67 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 134.84$, 130.02, 129.18, 128.51, 78.83; IR (neat): υ 3035, 2923, 2853, 1496, 1455, 1218, 771, 700, 591 cm^{-1}; GC-MS: $C_7H_7Cl_2N$: *m/z* 175[M]$^+$; HRMS: 174.99546 (calcd. 174.99555).

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ORCID

Vinodkumar Sriramoju http://orcid.org/0000-0002-2303-6693
Srinivas Kurva http://orcid.org/0000-0001-9665-9093
Sridhar Madabhushi http://orcid.org/0000-0001-7279-7846

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