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# PhI(OAc)<sub>2</sub>/NaX-mediated halogenation providing access to valuable synthons 3-haloindole derivatives<sup>†</sup>

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This paper describes a mild phenyliodine diacetate mediated method for selective chlorination, bromination, and iodination of indole C–H bonds using sodium halide as a source for analogous halogenations. The combination of NaX and phenyliodine diacetate provides an invincible system for halogenation of indoles. This protocol was compatible with a wide array of indole substrates and provides straight forward access to potential halogenated arenes.

Indoles are ubiquitous in marketed drugs and stand as a privileged scaffold in biologically active natural products.<sup>1</sup> Functionalized indoles are of paramount importance in chemical synthesis; in particular, 3-haloindoles are widely recognized as valuable intermediates/prefunctionalized starting materials in cross-coupling reactions.<sup>2</sup> The most appropriate strategy for the synthesis of the functionalized indole framework is through halogenations and subsequent cross-coupling methodologies or through direct C–H activation.<sup>3</sup> Recently 3-chloroindoles in conjunction with methyl coumalate have been demonstrated to generate carbazoles and 3-haloindoles to 3-(azol-1-yl)indoles, providing simple access to heterocycles under metal-free conditions.<sup>4</sup> Despite the utility of these compounds, installing halogen atoms, especially bromine and iodine, due to their high reactivity relative to chlorine on aromatic structures, is highly desirable.<sup>5</sup>

The most common approach to halogenated arenes is electrophilic aromatic substitution (EAS) using reagents such as *N*-halosuccinimides,  $X_2$  and peroxides with HX/MX.<sup>6</sup> Due to the clear limitations of the current methods, the development of an efficient, safe, simple and selective protocol for the formation of C–Cl, C–Br and C–I bonds is challenging but at the same time very attractive. In recent times, the oxidative halogenation by metal halides has emerged as an important alternative for the synthesis of halo compounds.<sup>7</sup> In this context phenyliodine diacetate was chosen as the best oxidant on the basis of the availability and ease of handling of hypervalent iodine(m) compounds.<sup>8</sup> Chlorination of arenes has been reported using the hypervalent iodine(m) reagent 1-chloro-1,2-benziodoxol-3-one as a chloro source (Scheme 1A).<sup>9</sup> The combination of hypervalent iodine reagents with metal halides as the halide source has been less explored for halogenations.<sup>10</sup> More recently Rh(m)-catalyzed halogenations of arylpyridines with PhI(OAc)<sub>2</sub>/NaX have been reported.<sup>11</sup> Therefore, it is appealing to develop simple reagents/systems without using metal catalysts.

Our previous study revealed that chlorination of MBH adducts could be easily achieved in high yields with the NaCl/oxone system in water.<sup>12</sup> This suggested that NaCl could be a better halo source as it is more economic, and readily activated to allow the halogenation of arenes under mild, atom economical, metal-free and environmentally benign conditions. We undertook a study of

#### (A) Previous Iodine (III) reagent mediated chlorination



(B) Present work: NaX/ PhI(OAc)<sub>2</sub> for C-H halogenation



Scheme 1 Halogenation reaction of indoles.





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 Table 1
 Optimization of reaction conditions<sup>a</sup>

	18			
			3a, X = Br 4a, X = I	
Entry	Oxidant	Salt	Solvent	Yield <sup>b</sup> (%)
1	Oxone	NaCl	H <sub>2</sub> O	_
2	TBHP	NaCl	$H_2O$	—
3	$H_2O_2$	NaCl	$H_2O$	—
4	$K_2S_2O_8$	NaCl	$H_2O$	—
5	PIDA	NaCl	$H_2O$	—
6	PIDA	NaCl	1,4-Dioxane	30
7	PIDA	NaCl	CH <sub>3</sub> CN	50
8	PIDA	NaCl	DCE	20
9	PIDA	NaCl	CH <sub>3</sub> CN:H <sub>2</sub> O	72
10	PIDA	NaCl	1,4-Dioxane : H <sub>2</sub> O	40
11	PIDA	NaCl	DCE: H <sub>2</sub> O	30
12	Oxone	NaCl	$CH_3CN: H_2O$	25
13	PIDA	NaBr	$CH_3CN: H_2O$	78
14	PIDA	NaI	$CH_3CN: H_2O$	91

<sup>*a*</sup> Reaction conditions: substrate **1a** (1.0 mmol), oxidant (1.0 mmol), sodium salt (1.0 mmol) and solvent (2.0 mL) at room temperature for 1-2 h. <sup>*b*</sup> Isolated yields.

the combination of NaX with phenyliodine diacetate for regioselective construction of C-X bonds at the C-3 position of indoles. This combination indeed acts as a very effective halogenating system for the C-H halogenations (chlorination,

**Table 2** Halogonation of indology with  $NaV/Dbl(OAc)^{a}$ 

bromination, and iodination) of various indoles under mild conditions (Scheme 1B).

#### Results and discussion

We commenced our studies by examining the reaction of indole as the model substrate with NaCl as a halogenating agent to investigate the optimal reaction conditions (Table 1). Treatment of indole (1 mmol) with oxone (1 mmol) and NaCl (1 mmol) in the presence of water as a solvent starting material was observed (entry 1). However, stoichiometric peroxy oxidants like TBHP, aq.  $H_2O_2$ ,  $K_2S_2O_8$  and hypervalent iodine(III) oxidant DIB were used in combination with NaCl in an aqueous system resulting in no reaction (entries 2-5). Furthermore, 1,4-dioxane, CH<sub>3</sub>CN and DCE were used as solvents and the desired product was observed in a 50% yield in the acetonitrile system with PIDA (entries 6-8). Indole C-3 substitution was identified by its <sup>1</sup>H NMR spectrum as the sole product/major product. Encouraged by this result, it was of interest to develop a green version of this useful halogenation process for which we used a combination of water with organic solvents in 1:1 ratios. To our surprise, 3-chloro indole was obtained in a high yield (72%) in the CH<sub>3</sub>CN:H<sub>2</sub>O system compared to other mixtures (entries 9-11). Hence, entry 9 was chosen as the perfect optimized conditions for C-3 chlorination with a 72% yield in the presence of hypervalent iodine(m) and diacetoxyiodobenzene PhI(OAc)2 with 1.0 equiv. of NaCl in

	acception of indoles						
			PhI(OAc) <sub>2</sub> laX (X = Cl, Br, I) CH <sub>3</sub> CN:H <sub>2</sub> O	X 2a-2j, X = Cl 3a-3l, X = Br 4a-4m, X = I			
					Yield <sup>b</sup> (	%)	
Entry	Substrate 1	Product (2a-2j)	Product (3a–3l)	Product (4a-4m)	2	3	4
1		Ci PH 2a	Br Br 3a	l → ↓ 4a	72	78	91
2	F	FUNCION 2b	F	F H 4b	62	61	75
3	CI CI	CI	CI N 3c	CI	67	69	82
4	Br	Br	Br Br 3d	Br	64	65	85
5	I T	Line Cl Representation of the second	Br N H H	I ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓	74	79	89
6	O <sub>2</sub> N	O <sub>2</sub> N N H 2f	O <sub>2</sub> N N N N N Sf 3f	$O_2N$ $H$ 4f	65	59	68
7	Z Z H	↓↓↓↓ H 2g	Br N H	↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓	79	82	94
8	MeO	MeO N H 2h	MeO NeO H Sh	MeO	78	81	92



<sup>*a*</sup> Reaction conditions: substrate **1a** (117 mg, 1.0 mmol), PhI(OAc)<sub>2</sub> (322 mg, 1.0 mmol), NaCl (58 mg, 1.0 mmol)/NaBr (103 mg, 1.0 mmol)/NaI (150 mg, 1.0 mmol) and CH<sub>3</sub>CN: H<sub>2</sub>O (1:1) (2.0 mL) at room temperature for 1–2 h. <sup>*b*</sup> Isolated yields were provided.

 $CH_3CN: H_2O$  (1:1) as a solvent. However, the reaction was very slow with a 25% yield in the presence of oxone in the  $CH_3CN:$  $H_2O$  system (entry 12). Interestingly NaBr and NaI also afforded C-3 bromination and iodination of indoles with 78% and 91% yields successively in the presence of PhI(OAc)<sub>2</sub> (entries 13 and 14).

To confirm the scope of the chlorination reaction, we attempted to apply the reaction to a variety of indoles under the optimized conditions. As a result, the present reaction is applicable to a wide range of substituted indoles, and these results are summarized in Table 2. The effect of substituents of both electron-donating and electron-withdrawing groups at the 5-position of the indole ring was considered. The results proved that the electronic characteristics of substituents on the aromatic ring have no considerable influence on the reaction yields. The chlorination reaction of indoles, having withdrawing substituents at their 5-position, smoothly proceeded and afforded the corresponding 3-chlorinated products (entries 2–6).

The results showed that C-5 substituted with an electron donating group afforded the corresponding monohalogenated products with very good yields (entries 7 and 8). However, in the case of *N*-phenyl substituted indoles, chlorination also proceeds regioselectively at the C-3 position with a low yield (entry 10).

In addition, bromination of the indole derivatives was studied, employing NaBr as a halogen source (Table 2). The substituted indole substrates with Me, OMe and F, Cl, Br, I, or NO<sub>2</sub> at the 5-position reacted to give the corresponding C-3 brominated products **3a-i** in 59–82% yields. The same results were obtained *via* phenyl, benzyl and methyl substitution at the N-1 position of indoles (entries 10–12).

Finally, iodination of indole derivatives was investigated in the presence of NaI as a halogen source (Table 2). The studied substrates showed a high selectivity, affording mono iodinated compounds **4a–m** in high yields (68–94%). Thus we found that the method is widely applicable to construct C–Cl, C–Br and C–I bonds of indoles with high regioselectivity.

Furthermore, we extended our study with heterocycles such as pyrrole, furan, thiophene and imidazole. Among them only imidazole gave the desired chloro and bromo products under the optimized reaction conditions and the results have been included in Table 3.

**Table 3** Halogenation of heterocycles with  $NaX/PhI(OAc)_2^{a,b}$ 

Entry	Compound	Product	$\operatorname{Yield}^{b}(\%)$
1		_	_
2		_	_
3	∠	_	_
4	N N N N N N N N N N N N N N N N N N N	N N H 5a	88
5	N N N N N N N N N N N N N N N N N N N	N N H 5b	90

<sup>*a*</sup> Reaction conditions: imidazole (68 mg, 1.0 mmol),  $PhI(OAc)_2$  (322 mg, 1.0 mmol), NaCl (58 mg, 1.0 mmol)/NaBr (103 mg, 1.0 mmol) and  $CH_3CN:H_2O$  (1:1) (2.0 mL) at room temperature for 1–2 h. <sup>*b*</sup> Isolated yields were provided.





It has been reported that the treatment of TiCl<sub>4</sub> with 1,3-dicarbonyl compounds results in the formation of complexes, with concomitant release of halide ions.13 Then addition of DIB to the reaction mixture results in an exchange of the acetate by the chloride ion to generate a mixed-ligated  $\lambda^3$ -iodane of type 5, which is labile, presumably due to the unfavorable combination of Cl/OAc trans influences (Scheme 2).<sup>14</sup> A similar *in situ* generated bromoiodinane from PIDA and LiBr has been recently postulated as a brominating agent of arenes.<sup>15</sup> The corresponding Br<sup>+</sup> and I<sup>+</sup> are generated from readily available halide salts (TBAB, KI) in situ, upon oxidation with Selectfluor.<sup>16</sup> In order to investigate whether 5 is an intermediate in our halogenation studies we conducted the experiment with stable benziodoxole 6 in the absence of DIB (Scheme 2).<sup>10d</sup> We have found that indoles were chlorinated indicating that 5 is the possible intermediate in this pathway.

As for the mechanism, Corey has determined experimentally that the reaction of  $PhI(OAc)_2$  with KBr generates  $Br_2$ .<sup>17</sup> A positive halogen species is generated under the reaction conditions by oxidation of halide ions with  $PhI(OAc)_2$ . Then the halide cation is attacked by the electron-rich indoles **1** highly regioselectively at the C-3 position to form intermediate **A** or its resonance **B** which on loss of protons gives the corresponding halo product **2a** (Scheme 3).

#### Conclusions

In summary, we have developed a synthetically useful C-3 selective C–H halogenation reaction of indoles. Inexpensive NaCl as a halogen source and PIDA as an oxidant are significant practical advantages of this protocol. Moreover, the method is compatible for chlorination, bromination and iodination of indoles bearing diverse functional groups. The halogenated products of this fast-track strategy represent a class of valuable synthons for step economical synthesis of many bioactive molecules, as well as marketed drugs. This methodology overcome the limitations associated with conventional metal catalysts and enables regioselective C-3 halogenation of indoles.

## Conflicts of interest

There are no conflicts to declare.

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