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Eco-friendly oxyiodination of aromatic compounds using ammonium iodide and hydrogen peroxide[☆]

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Abstract—A new eco-friendly procedure for the oxyiodination of aromatic compounds with NH_4I as an iodine source and H_2O_2 as an oxidant without any catalyst is presented.

Aryl iodides are important intermediates in organic synthesis, medicine and biochemistry.[1] They are also valuable and reactive intermediates for various cross-coupling reactions,[2] for example, Heck, Stille and Negishi cross-coupling reactions.

The use of molecular halogens for direct halogenation involves difficulties in handling chlorine and bromine, while iodine is less reactive. The poor electrophilic strength of iodine, compared to that of molecular bromine and chlorine, renders direct iodination difficult and requires the presence of an activating agent in order to produce a strongly electrophilic $I^{\oplus}$ species. Direct iodination is also hampered by the formation of HI, which can cause proteolytic cleavage of sensitive compounds. Iodination of aromatic compounds has been carried out using molecular iodine together with strong oxidizing agents such as nitric acid, sulfuric acid, iodic acid, sulfur trioxide and hydrogen peroxide.[3] Recently, iodination methods have been developed using iodonium donating systems, such as iodine nitrogen dioxide,[4] mercury(II) oxide–iodine,[5] iodine monochloride,[6] bis(pyridine) iodonium(I) tetrafluoroborate–CF_3SO_3H,[7] NaOCl–NaI,[8] iodine/$Na_2S_2O_8$,[9] iodine–$(NH_4)_2S_2O_8$–$CuCl_2$–Ag_2SO_4,[10] I_2–tetrabutylammonium peroxydisulfate,[11] I_2–diiodine pentoxide,[12] I_2–lead acetate,[13] I_2–thallium acetate,[14] I_2–F–TEDA–BF_4,[15] BuLi–F_3CCH_2I,[16] KI-oxone®,[17] bis(symcollidine)-iodine(I) hexafluorophosphate,[18] $KI/H_2O_2/H_2SO_4$,[19] $ICl/In(OTf)_3$,[20] HIO_4/Al_2O_3,[21] NIBTS,[22] NaI/Chloramine-T,[23] KI/H_2O_2 or sodium perborate/sodium tungstate,[24] $I_2/O_2/H_5PV_2Mo_{10}O_{40}$,[25] $KI/KIO_3/H^+$,[26] I_2/UHP[27] and NaI/cerium(IV) trihydroxide/SDS.[28] Most of these reagents are complicated, costly or use toxic heavy metal catalysts with potential environmental problems due to the generation of hazardous waste.

Regarding environmental problems and pollution, clean organic reaction processes which do not use harmful organic reagents are encouraged and are in great demand. The role of enviro-economics in the development of new processes for existing and new products has become important. Hydrogen peroxide has enormous potential as a green oxidant from which the only waste product is water.[29] There are hazards connected with the use of concentrated solutions but this risk can be avoided by employing 30% aqueous H_2O_2. However, oxidative halogenation of arenes requires the use of a metal catalyst for activation.[30] The non metal-catalyzed oxidative iodination of aromatic compounds with H_2O_2 without addition of mineral acid has not been reported so far. Our aim was to utilize 30% H_2O_2 for the iodination of arenes with NH_4I without addition of any metal catalyst or mineral acid.

We have designed an efficient, environmentally benign procedure for aromatic iodination using NH_4I as an iodine source and commercially available 30% H_2O_2 as an oxidant and as a possible alternative to overcome the disadvantages described in the reported methods (Scheme 1).

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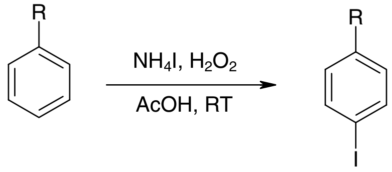


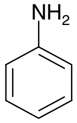
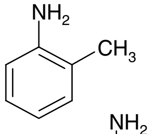
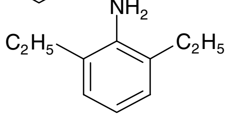
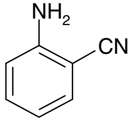
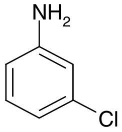
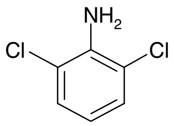
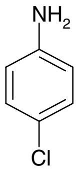
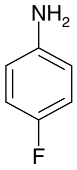
Scheme 1.

General procedure for the iodination of aromatic compounds: a 30% aqueous solution of H_2O_2 (2.2 mmol) was added dropwise to a well stirred solution of NH_4I (2.2 mmol) and aromatic substrate (2 mmol) in acetic acid (4 ml) and the reaction mixture was allowed to stir at room temperature. The reaction was monitored by thin layer chromatography (TLC). After completion, the reaction mixture was filtered and the filtrate was treated with sodium thiosulfate and extracted with ethyl acetate. The organic extract was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The products were purified by column chromatography and their structures confirmed by ^{1}H NMR and mass spectroscopy.

The results of the iodination of a wide range of aromatic compounds are given in Table 1. The reaction of aromatic compounds with NH_4I and 30% H_2O_2 in acetic acid at room temperature afforded iodo compounds with high regioselectivity and in excellent yields.

Deactivated and weakly activated compounds failed to undergo iodination, whereas more activated compounds, that is, anilines, substituted anilines, phenols, substituted phenols and methoxynaphthalenes were

Table 1. Oxyiodination of aromatic compounds with NH_4I and H_2O_2 in acetic acid[a]

Entry	Substrate	Time (h)	Conversion (%)	Selectivity[b] (%)			
				para	*ortho*	Di	Others
1		8	82	97	3	—	—
2		8	88	77	23	—	—
3		8	69	99	—	—	—
4		24	93	99	—	—	—
5		8	38	61	39	—	—
6		24	42	99	—	—	—
7		8	99	—	85	5	10
8		8	99	—	75	5	20

(*continued on next page*)

Table 1 (*continued*)

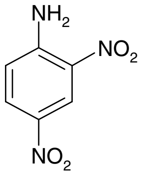
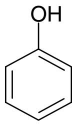
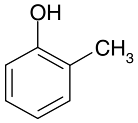
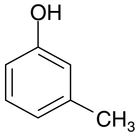
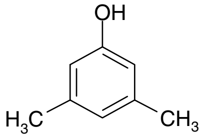
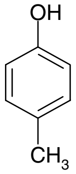
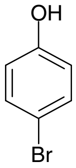
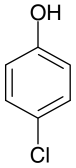
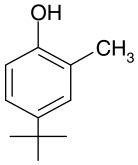
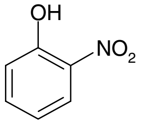
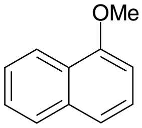
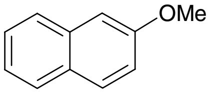
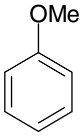
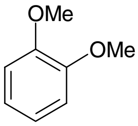
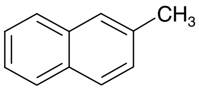
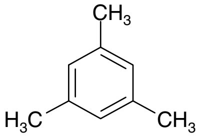
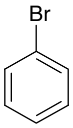
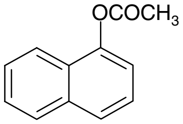
Entry	Substrate	Time (h)	Conversion (%)	Selectivity^b (%)			
				para	*ortho*	Di	Others
9		24	—	—	—	—	—
10		6	78	53	47	—	—
11		6	70	55	40	5	—
12		6	73	56	42	2	—
13		6	72	66	34	—	—
14		6	84	—	93	4	3
15		6	73	—	99	—	—
16		6	70	—	95	—	5
17		6	87	—	99	—	—
18		24	—	—	—	—	—

Table 1 (*continued*)

Entry	Substrate	Time (h)	Conversion (%)	Selectivity[b] (%)			
				para	*ortho*	Di	Others
19		6	98	99	—	—	—
20		6	82	—	99[c]	—	—
21		24	—	—	—	—	—
22		24	—	—	—	—	—
23		24	—	—	—	—	—
24		24	—	—	—	—	—
25		24	—	—	—	—	—
26		24	—	—	—	—	—

[a] Substrate (2 mmol), NH_4I (2.2 mmol), 30% H_2O_2 (2.2 mmol), acetic acid (4 ml), rt.

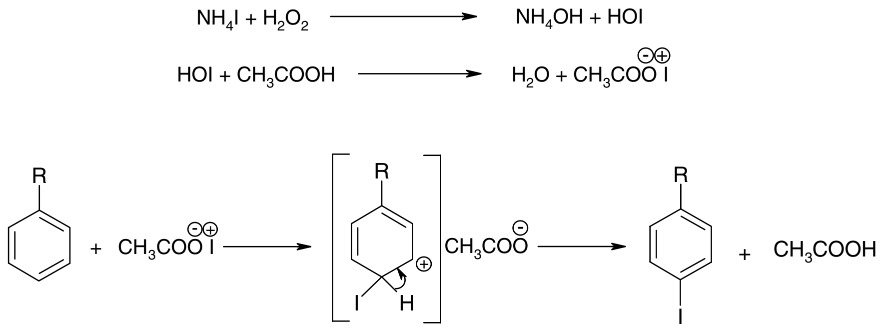
[b] The products were characterized by ^{1}H NMR and mass spectroscopy and quantified by GC.

[c] 1-Iodo-2-methoxynaphthalene.

converted into the corresponding iodinated products. Surprisingly, methoxybenzene derivatives, despite their marked activity in electrophilic reactions, were not iodinated.

The results also indicate that activated aromatic compounds are more selective for nuclear iodination and no side-chain iodination was observed in the case of alkyl substituted aromatics (Table 1, entries 2, 3, 11–14 and 17). Introduction of an electron-withdrawing group on the aromatic ring substantially decreased the rate of ring iodination (Table 1, entry 4). Unless the *para*-position is substituted, this reaction system yields, selectively, *para*-iodinated aromatics with anilines, while with phenols, substantial amounts of *ortho* substituted aromatics were also formed. The *para* substituted aromatics were iodinated at the *ortho*-position (Table 1, entries 7, 8 and 14–17).

We have also studied the influence of a wide-range of solvents including carbon tetrachloride, hexane, dichloromethane, chloroform, methanol, acetonitrile and acetic acid on the reactivity. Our observations revealed that, among the various solvents, acetic acid was the most effective, giving high yields in short reaction times. The rate of the reaction was increased by using acetic acid. It was assumed that acetic acid forms an intermediate species $CH_3COO^{\ominus}I^{\oplus}$ (Scheme 2), which facilitates easy generation of $I^{\oplus}$. The role of hydrogen peroxide was confirmed by conducting a blank experiment where formation of the iodo compound was not observed.



Scheme 2.

A plausible mechanism for the iodination of aromatic compounds is shown in Scheme 2. It is assumed that hydrogen peroxide oxidizes the $I^{\ominus}$ (NH_4I) to $I^{\oplus}$ (HOI), which further reacts in the presence of acetic acid (Brønsted acid) with the organic substrate to give the corresponding iodinated product.

In conclusion, we have reported a practical, efficient, relatively inexpensive and eco-friendly method for iodination of aromatic compounds using commercially available NH_4I and H_2O_2. This method can be applied to a wide range of aromatic compounds with moderate to high regioselectivity.

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