

Peroxide/Potassium Iodide Redox Systems for *in situ* Oxyiodination of Organic Compounds under Liquid-Phase and Solvent-Free Conditions

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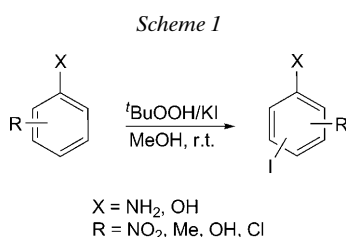
Iodination of certain aromatic amines and phenols are triggered by the oxidation of KI by peroxy compounds such as *tert*-butyl hydroperoxide (*t*BuOOH) under liquid-phase and solvent-free conditions by grinding the reactants in a mortar with a pestle. The reactions afforded corresponding iodo derivatives in good yield with high regioselectivity (*Table 1*).

Introduction. – Iodinated organic molecules are important compounds in synthetic chemistry and are used widely in pharmaceutical and chemical industries creating a high demand for efficient and economical methods for their production [1]. In the recent past, there has been an enhanced interest in the study of halogenated aromatic compounds because of their use as intermediates for the synthesis of natural products and bioactive materials [2]. Aromatic iodides are important building blocks in modern organic synthesis especially for C–C bond-formation *via* cross-coupling reactions [3]. Several methods for the direct introduction of halogen atoms into aromatic molecules have been widely developed especially during the past decade. Iodoarenes are often used in the synthesis of alkenylarenes, and other classes of compounds. In recent years, direct iodination methods have been intensively investigated by using iodonium-donating systems, such as $\text{NH}_4\text{I}/\text{Oxone}^\circledast$ [4], $\text{I}_2/(\text{Bu}_4\text{N})_2\text{S}_2\text{O}_8$ [5][6], I_2/AlCl_3 and CuCl_2 [7], I_2/AgNO_3 [8a], $\text{I}_2/\text{F-TEDA-BF}_4$ (= 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) [8b], $\text{I}_2/(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$ [9][10], $\text{I}_2/\text{N,N}$ -diethylaniline/borane [11], $\text{I}_2/\text{Cr}_2\text{O}_3$ [12], I_2/silen (= $\text{SiO}_2/\text{Fe}(\text{NO}_3)_3 \cdot 9 \text{H}_2\text{O}$) [13], $\text{NaI}/\text{chloramine-T}$ *N*-chloro-4-methylbenzenesulfonamide sodium, salt [14], KI/HIO_4 in H_2SO_4 [15], *etc.* However, many of them suffer from a lack of regioselectivity of iodination of activated aromatic compounds, so that control over the degree of iodination and regioselectivity is still needed. *tert*-Butyl hydroperoxide (*t*BuOOH) has been employed as novel oxidizing agent in the synthesis of organic compounds [16–19]. *t*BuOOH is a safe, effective, selective, and widely used versatile oxidant employed under mild conditions.

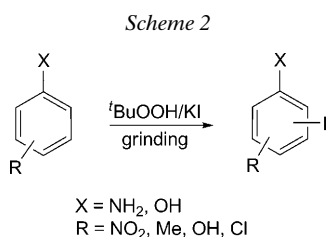
The chemists' concern for developing environmentally friendly synthetic procedures has prompted them to turn their attention to minimize or circumvent the use of solvents that are one major cause of pollution. This has led, in recent times, to extensive research activity and reinvestigation of known reactions to achieve organic synthesis under solvent-free conditions. The latest reviews and publications [20–24] show the importance of solvent-free organic syntheses and underline that these procedures are

not only simple but also satisfy both economical and environmental demands by replacing problematic solvents. Solvent-free reactions obviously reduce pollution and bring down handling costs due to the simplification of experimental procedures, workup techniques, and labor saving. Encouraged by these aspects, we report herein our results on the iodination of a representative range of phenols and aromatic amines under solvent-free and solution-phase conditions. A solvent-free or solid-state reaction can be carried out with the reactants alone or incorporating them in clays, zeolite, silica, alumina, or other matrices. A thermal process or irradiation with UV, microwave, or ultrasound can also be employed to bring about a reaction. However, in the present study, a solvent-free iodination of aromatic amines and phenols was performed by grinding the reactants in a mortar with a pestle.

Experimental. – *General Procedure for Iodination of Phenols and Aromatic Amines in Solution.* ^tBuOOH (2 mmol) was added to a well-stirred soln. of KI (4 mmol), the substrate (2 mmol), and one drop of acid in MeOH (20 ml) at r.t. (*Scheme 1*). After the completion of the reaction (TLC monitoring), the mixture was quenched with 2% aq. Na₂S₂O₃ soln. and then extracted with AcOEt. The org. phase was dried (Na₂SO₄) and concentrated and the residue purified by column chromatography (CC; SiO₂, AcOEt/hexane 1:4).



General Procedure for Iodination of Phenols and Aromatic Amines under Solvent-free Conditions. ^tBuOOH (0.1 mol), KI, (0.2 mol), and the substrate (0.10 mol) were placed in a mortar and ground with a pestle (*Scheme 2*). After completion of the reaction (TLC monitoring), the mixture was dissolved in CHCl₃ and quenched with Na₂S₂O₃ soln. The org. layer was dried (Na₂SO₄) and concentrated and the residue purified by CC (SiO₂, AcOEt/hexane 3:7).



Results and Discussion. – The solvent-free oxyiodination with ^tBuOOH/KI is a mild method for the highly regioselective introduction of an iodo substituent in various activated and deactivated aromatic compounds such as phenols or aromatic amines under neutral conditions. For this, ^tBuOOH, KI and the aromatic compound were ground in a mortar with a pestle affording the corresponding iodo derivatives in good yields (*Table 1*). Thus, the direct iodination of a wide range of aromatic compounds

Table 1. Iodination of Aromatic Amines and Phenols with *t*BuOOH/KI

Substrate	Product	MeOH		Solvent-free	
		Time [h]	Yield [%]	Time [min]	Yield [%]
Benzamine	4-Iodobenzenamine	2.0	65	40	62
4-Methylbenzenamine	2-Iodo-4-methylbenzenamine	3.5	60	40	54
4-Chlorobenzenamine	4-Chloro-2-iodobenzenamine	3.5	68	40	65
4-Nitrobenzenamine	2-Iodo-4-nitrobenzenamine	3.0	95	60	58
Phenol	4-Iodophenol	2.5	64	40	56
2-Methylphenol	4-Iodo-2-methylphenol	2.5	62	45	59
4-Chlorophenol	4-Chloro-2,6-diiodophenol	4.0	77	40	66
4-Methylphenol	2,6-Diiodo-4-methylphenol	4.0	71	45	58
4-Nitrophenol	2,6-Diiodo-4-nitrophenol	3.5	74	45	60
Naphthalen-2-ol	1-Iodonaphthalen-2-ol	3.0	82	45	54
Chlorobenzene	1-Chloro-4-iodobenzene	2.5	65	40	55

Table 2. Spectroscopic Analysis of the Iodinated Products. δ in ppm, J in Hz.

	M^+	$^1\text{H-NMR}$ (CDCl_3)	M.p. [$^\circ$]	
			Present work	Lit. value
4-Iodobenzenamine	219	4.11 (<i>s</i> , NH_2), 6.44 (<i>d</i> , $J=8.7$, 2 H), 7.46 (<i>d</i> , $J=8.7$, 2 H)	62–63	63 [24a]
2-Iodo-4-methylbenzenamine	249	2.34 (<i>s</i> , Me), 4.22 (<i>br.</i> , NH_2), 6.23 (<i>d</i> , $J=8.2$, 1 H), 7.62 (<i>dd</i> , $J=8.2$, 2.6, 1 H), 8.18 (<i>d</i> , $J=2.6$, 1 H)	36–37	39–40 [24b]
4-Chloro-2-iodobenzenamine	253	4.02 (<i>br.</i> , NH_2), 6.58 (<i>d</i> , $J=8.9$, 1 H), 7.07 (<i>dd</i> , $J=8.9$, 2.0, 1 H), 7.58 (<i>d</i> , $J=2.0$, 1 H)	38–39	40–41 [24c]
2-Iodo-4-nitrobenzenamine	264	4.81 (<i>br.</i> , NH_2), 6.70 (<i>d</i> , $J=9.1$, 1 H), 8.07 (<i>dd</i> , $J=9.1$, 2.2, 1 H), 8.59 (<i>d</i> , $J=2.2$, 1 H)	100–101	106–107 [24d]
4-Iodophenol	204	4.72 (<i>br.</i> , OH), 6.62 (<i>d</i> , $J=8.3$, 2 H), 7.53 (<i>d</i> , $J=8.3$, 2 H)	89–90	92–93 [24e]
4-Iodo-2-methylphenol	222	2.32 (<i>s</i> , Me), 5.12 (<i>s</i> , OH), 6.54 (<i>d</i> , $J=8.6$, 1 H), 6.72 (<i>dd</i> , $J=8.6$, 2.9, 1 H), 7.46 (<i>d</i> , $J=2.9$, 1 H)	62–64	66.5–68 [24f]
4-Chloro-2,6-diiodophenol	379	5.12 (<i>s</i> , OH), 7.32 (<i>s</i> , 2 H)	103–104	108 [24g]
2,6-Diiodo-4-methylphenol	360	2.26 (<i>s</i> , Me), 5.45 (<i>s</i> , OH), 7.48 (<i>s</i> , 2 H)	55–56	60–61 [24h]
2,6-Diiodo-4-nitrophenol	391	5.12 (<i>s</i> , 1 H), 7.75 (<i>s</i> , 2 H)	151–152	155.5 [24i]
1-Iodonaphthalen-2-ol	270	5.67 (<i>br.</i> , OH), 6.89 (<i>d</i> , $J=8.8$, 1 H), 7.35 (<i>d</i> , $J=8.0$, 1 H), 7.69 (<i>t</i> , $J=7.6$, 1 H), 7.78 (<i>m</i> , 2 H), 8.18 (<i>d</i> , $J=8.0$, 1 H)	87–89	91–93 [24j]
1-Chloro-4-iodobenzene	238 (100%), 240 (35%)	7.10 (<i>d</i> , $J=7.9$, 2 H), 7.62 (<i>d</i> , $J=7.9$, 2 H)	52–53	57 [24k]

substituted with electron-donating groups such as MeO, OH, or NH₂ groups was achieved efficiently with high regioselectivity under mild conditions.

The structure of the products was confirmed by ¹H-NMR and MS data (Table 2).

In conclusion, the results indicate that the substrates generally underwent monoiodination. However, phenols appeared to have undergone diiodination. The yields of the products obtained by the described solvent-free protocol are good; hence, the methodology could be used for the iodination of organic compounds.

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