Highly selective iodination of phenols using potassium iodide and benzyltriphenylphosphonium peroxymonosulfate

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An easy and selective method for monoiodination of phenols using potassium iodide in the presence of benzyltriphenylphosphonium peroxymonosulfate is presented. The reactions have been carried out in acetonitrile to afford the corresponding iodophenols in moderate to high yields.

Keywords: benzyltriphenylphosphonium peroxymonosulfate, iodination, potassium iodide, phenols

Aromatic iodides especially iodophenols have widely been used in radiolabelling studies, and also as synthetic intermediates in the formation of new carbon–carbon or carbon–heteroatom bonds via replacement of their iodine atoms with electrophiles.[1] Despite the importance of iodophenols, there are few good methods in the literature for iodination of phenols. Conventional methods for aromatic iodination imply the use of molecular iodine together with highly toxic heavy metal compounds, or mineral acids which is undesirable from the environmental point of view.[2] Reactions such as $I_2/AlCl_3$-$CuCl_2$,[3] $I_2/SbCl_5$,[4] $NH_4I/O_2/NOBF_4/CF_3COOH/CH_2Cl_2$ or CF_3COOH/CH_3COOH,[5] $ICl/Cp_2FeB[3,5\text{-}(CF_3)_2C_6H_3]_4/DDQ$,[6] $PhCH_2NEt_3ICl_2/NaHCO_3$,[7] IPy_2BF_4,[8] $I_2/Pb(OAc)_4$,[9] NIS/CF_3SO_3H,[10] N-iodosaccharin[11] and IF[12] have been reported in recent years. However, some of the existing methods have associated environmental hazards with respect to handling and storage of molecular iodine, strongly acidic conditions, expensive and complex catalysts, toxic metallic compounds and rare oxidising reagents that are difficult to prepare. Therefore, there is a need for a simple, less expensive, and safer method for iodination of phenols. Halide salts are safer commodities and can be used for this purpose.[13]

Peroxymonosulfate ion, HSO_5^-, is a versatile anionic oxidant which is usually used as Oxone ($2KHSO_5.KHSO_4.K_2SO_4$).[14] This triple salt is an inexpensive, water-soluble and stable oxidising reagent that is commercially available, but it is insoluble in organic solvents and buffering is needed due to its acidity.[14] Recently, we have reported benzyltriphenylphosphonium peroxymonosulfate **1** ($PhCH_2Ph_3PHSO_5$) as a mild, inexpensive and efficient oxidising reagent for the oxidation of organic compouns.[15]

In the course of our studies on the halogenation of organic compounds,[16] we investigated the selective iodination reactions of phenols **2** employing potassium iodide in the presence of the oxidant **1** under non-aqueous conditions. This constitutes a mild and selective method to prepare iodophenols **3** containing even electron-withdrawing substituents.

Benzyltriphenylphosphonium peroxymonosulfate **1**, a mild, efficient, stable and cheap reagent, is a white powder, which is quite soluble in dichloromethane, chloroform, acetone and acetonitrile and insoluble in non-polar solvents such as carbon tetrachloride, *n*-hexane and diethyl ether. This reagent is readily prepared by the dropwise addition of an aqueous solution of Oxone to an aqueous solution of benzyltriphenylphosphonium chloride in quantitative yield at room temperature and could be stored for months without losing its potency.[15] The amounts of HSO_5^- in this reagent have been determined by an iodometric titration method[17] and the measurements are consistent with almost 99% by weight of active oxidising agent.

We have reported a selective method for iodination of phenols **2**, affording iodophenols **3** in *para* substituent where possible, in moderate to high yields. Our method is based on the *in situ* oxidation of potassium iodide using **1** in acetonitrile. Simply by adding reagent **1** to a solution of the phenol **2** and potassium iodide in acetonitrile, rapid and selective iodination is achieved at room temperature. The products can be separated by straightforward workup. In some instances, the products crystallise and may be isolated by filtration. The method has been applied successfully to a variety of phenols **3** (Table 1).

At first, the iodination of 2,6-dimethylphenol **2c** as the model compound using potassium iodide and 1 in various solvents was examined. The solvents examined were dichloromethane, chloroform and acetonitrile. The reactions were carried out by stirring **2c** with 1 and KI (1:1) at room temperature. Dichloromethane and chloroform were inferior solvents to acetonitrile, because the reaction stopped at lower conversions in these solvents than that in acetonitrile. Next, the effects of the amount of the oxidant **1** and KI were examined with **2c** (1 mmol) under non-aqueous conditions in

Table 1 Iodination of phenols **2** using KI in the presence of $PhCH_2Ph_3PHSO_5$ **1** in aprotic solvent[a,b]

Entry	Substrate	Product **3**	Time/h	Yield[c]/%	M.p. or b.p. °C/torr	
					Found	Reported[18]
2a	2-Naphthol	1-Iodo-2-naphthol	2	91	93–94	94.5
2b	$2,4\text{-}(Me)_2C_6H_3OH$	$6\text{-}I\text{-}2,4\text{-}(Me)_2C_6H_2OH$	2	90	122–123/16	123–124/16
2c	$2,6\text{-}(Me)_2C_6H_3OH$	$4\text{-}I\text{-}2,6\text{-}(Me)_2C_6H_2OH$	1.5	88	101–102.5	102–102.5
2d	$2,3\text{-}(Me)_2C_6H_3OH$	$4\text{-}I\text{-}2,3\text{-}(Me)_2C_6H_2OH$	2	80	81–83	82–83
2e	$2\text{-}MeC_6H_4OH$	$4\text{-}I\text{-}2\text{-}MeC_6H_3OH$	2	85	66.5–68	66–68
2f	$3,5\text{-}(Me)_2C_6H_3OH$	$4\text{-}I\text{-}3,5\text{-}(Me)_2C_6H_2OH$	1.5	78	135–138	135–136
2g	$2\text{-}Cl\text{-}5\text{-}MeC_6H_3OH$	$2\text{-}Cl\text{-}4\text{-}I\text{-}5\text{-}MeC_6H_2OH$	3	80	59–61	–
2h	$4\text{-}NO_2C_6H_4OH$	$2\text{-}I\text{-}4\text{-}NO_2C_6H_3OH$	6	80	85–87	86–87
2i	$2,5\text{-}(NO_2)_2C_6H_3OH$	$4\text{-}I\text{-}2,5\text{-}(NO_2)_2C_6H_2OH$	12	75	112	111–112
2j	$2,5\text{-}(Me)_2C_6H_3OH$	$4\text{-}I\text{-}2,5\text{-}(Me)_2C_6H_2OH$	2	86	96–98	98
2k	$2\text{-}NO_2C_6H_4OH$	$4\text{-}I\text{-}2\text{-}NO_2C_6H_3OH$	5	84	80–82	80–81

[a]Confirmed by comparison with known samples.
[b]Substrate/KI/oxidant (1:1:1).
[c]Yield of isolated pure product after purification.

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acetonitrile. The optimum molar ratio of substrate to KI to oxidant **1** (1:1:1) was determined for complete conversion of phenols **2** to monoiodinated products **3**. It should be noted that in the absence of **1** no conversion of substrate to product occurred after 24h. By using this method, a wide variety of phenols **2** were iodinated to the corresponding monoiodinated products **3** in moderate to high yields within short reaction periods (Table 1 and Scheme 1). The products were isolated by filtering the reaction mixture and washing the filtrate with 5% $NaHSO_3$, drying over Na_2SO_4, and concentrating. The crude products were recrystallised in an appropriate solvent for crystalline products. This method offers a simple, general, selective and highly efficient route for converting phenols **2** to the corresponding iodophenols products **3**. To evaluate the utility of this procedure for large scale, a 10-fold scale iodination was carried out with 1 for the iodination of 2-naphthol **2a**, and the corresponding 1-iodo-2-naphthol **3a** was obtained in 91% yield within 2h.

In conclusion, this new method for converting phenols to iodophenols offers the following advantages: (a) the reagent **1** is a cheap, selective and safe oxidant, (b) the procedure is simple and occurs in aprotic solvent, (c) the yield of iodophenol is moderate to high (d) unlike previous iodination methods, this methodology did not require any transition metal complex, as catalyst.

Experimental

General: Yields refer to isolated products after purification. The products were characterised by comparing their spectral (IR, ^{1}H NMR), TLC, and physical data with those of authentic samples.[18] All ^{1}H NMR spectra were recorded at 90 MHz in $CDCl_3$ relative to TMS as an internal standard and IR spectra were recorded on Shimadzu 435 IR spectrometer. All reactions were carried out under aprotic conditions at room temperature. The reagent 1 was prepared according to our previous reported procedures.[15]

Iodination of phenols using KI in the presence of $PhCH_2Ph_3PHSO_5$; Typical procedure: To a solution of reagent 1 (10 mmol, 4.66 g) and potassium iodide (10 mmol, 1.66 g) in acetonitrile (50 ml) in a 250 ml round-bottomed flask, 2-naphthol 2a (10 mmol, 1.44 g) was added. The reaction mixture was stirred at room temperature for 2h. After disappearance of the starting phenol monitored by TLC using EtOAc/cyclohexane (2:8), the mixture was filtered through a sintered glass funnel, the solid residue was washed with acetonitrile (50 ml). The organic layers were combined and washed successively with 5% aqueous sodium bisulfite solution (100 ml), dried over Na_2SO_4 and concentrated. The crude product was recrystallised in ethanol to afford 1-iodo-2-naphthol **3a** as a needle solid in 91% yield, m.p. 93–94 °C [Lit.[18] m.p. 94.5 °C]; ^{1}H NMR ($CDCl_3$, 90 MHz): δ 5.80 (s, 1 H, OH), 7.20 (d, J = 8 Hz, 1 H, 3-H), 7.33 (t, J = 8 Hz, 1 H, 6-H), 7.50 (t, J = 8 Hz, 1 H, 7 H), 7.72 (m, 2 H, 4-H and 5-H), 7.92 (d, J = 9 Hz, 1 H, 8-H).

2,6-Dimethyl-4-iodophenol (**2c**): ^{1}H NMR ($CDCl_3$): δ 7.30 (s, 2 H, 3-H), 4.69 (s, 1 H, OH), 2.24 (s, 6 H, CH_3).

4-Iodo-2-methylphenol (**2e**): ^{1}H NMR ($CDCl_3$): δ 7.43 (d, 1 H, J = 2 Hz, 3-H), 7.33 (dd, 1 H, J_1 = 8 Hz, J_2 = 2 Hz, 5-H), 6.70 (d, 1 H, J = 8 Hz, 6-H), 4.70 (s, 1 H, OH), 2.20 (s, 3 H, CH_3).

2-Chloro-4-iodo-5-methylphenol (**2g**): ^{1}H NMR ($CDCl_3$): δ 7.73 (s, 1 H, 3-H), 6.80 (s, 1H, 6-H), 5.52 (s, 1H, OH), 2.30 (s, 3H, CH_3). Anal. Calcd. for C_6H_6ClIO: C, 28.07; H, 2.34. Found: C, 28.27; H, 2.45%.

2-Iodo-4-nitrophenol (**2h**): ^{1}H NMR ($CDCl_3$): δ 8.61 (d, 1 H, J = 2 H, 3-H), 8.10 (dd, 1 H, J_1 = 7 Hz, J_2 = 2 Hz, 5-H), 7.10 (d, 1 H, J = 7 Hz, 6-H), 6.22 (s, br, 1 H, OH).

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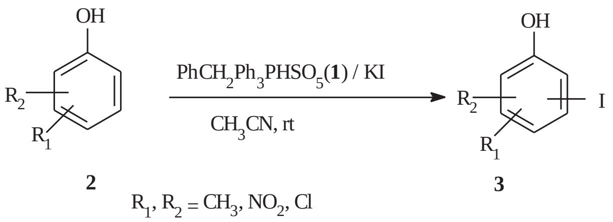

Scheme 1

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