'Green' Iodination of Dimethoxy- and Trimethoxy-Substituted Aromatic Compounds Using an Iodine–Hydrogen Peroxide Combination in Water

Jasminka Pavlinac,[a] Marko Zupan,[a,b] Stojan Stavber*[a]

[a] Laboratory for Organic and Bioorganic Chemistry, 'Jozef Stefan' Institute, Jamova 39, 1000 Ljubljana, Slovenia

[b] Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, 1000 Ljubljana, Slovenia
Fax +386(1)4773822; E-mail: Stojan.stavber@ijs.si

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Dedicated to Professor Miha Tišler on the occasion of his 80th birthday

Abstract: Mild iodination using iodine and a 30% solution of hydrogen peroxide as oxidant was performed in water. The method proved to be efficient and selective for the introduction of iodine into dimethoxybenzenes, trimethoxybenzenes, and dimethoxy- and trimethoxy-substituted acetophenones, thus significantly contributing toward a more environmentally friendly procedure than that previously reported.

Key words: green chemistry, iodine, halogenation, hydrogen peroxide, iodination in water

Iodo-substituted organic compounds have received significant attention in the scientific community.[1] Iodo-derivatives play an important role as synthons or as valuable precursors in organic synthesis,[2] mainly in C–C and C–N bond formation, which has been used for the synthesis of several natural products and bioactive compounds. Moreover, iodinated compounds can be used as radioactively labelled markers or contrastors in medical diagnosis.[3]

Due to the low reactivity of molecular iodine, considerable efforts have been put into the development of an efficient and mild method for direct introduction of iodine into organic molecules through an electrophilic reaction process. Intensive research over the years resulted in numerous diverse procedures using iodonium donating agents. In some of them rigorous conditions are applied, such as, extensive use of strong acids in combination with an iodinating agent (HNO_3/H_2SO_4, HIO_3, H_2SO_4, HIO_4/H_2SO_4, CF_3SO_3H),[4] or the use of heavy metal salts or oxides as activators of iodine (I_2/HgX_2, I_2/HgO, I_2/Ag_2SO_4, $I_2/Pb(OAc)_4/HOAc$).[5] Profound concerns over environmental issues, as well as high health risks are associated with the mentioned procedures. Some other reported methods employing less toxic reagents and milder conditions include I_2/F–TEDA–BF_4,[6] ICl,[7] NIS,[8] NaOCl–NaI,[9] $I_2/PhI(OAc)_2$,[10] but organic solvents are still required as reaction media.

Continuous growing concern over environmental pollution, health risks, and sustainable development has prompted chemists to search for greener methods to replace traditional ones. The concept of green chemistry emerged a decade ago and it is becoming increasingly important to apply the principles of green chemistry to every area of science.[11] Within organic chemistry, efficient catalytic methodologies compared to stochiometric reagents, utilization of renewable raw materials rather than fossil fuels as the basic feedstock, reactions involving the principle of atom economy, and the suitability of a safer alternative reaction medium in place of volatile organic solvents are some of the major and still challenging issues driven by the pressing need for environmentally more acceptable processes. Bearing this in mind and our continued interest in the development of 'greener' halogenation synthetic methods[12] we now report the application of the reaction system $I_2/H_2O_2/H_2O$[12b,13] for selective and efficient iodination of di- and trimethoxy substituted aromatic compounds. The chosen substrates either possess bioactive properties (anti-tumor or antioxidant activity), or mimic the structural fragment often present in bioactive compounds.[14] It is known that the introduction of a halogen atom can even enhance bioactivity in many cases.

Water, the most readily available medium, possesses several advantages over traditional organic solvents. Due to its non-toxicity and non-flammability, it is considered as the most benign reaction medium. In addition to its inexpensiveness and abundance, water as a reaction medium corresponds well to the current trends of green chemistry.[15] Although its application was much underestimated in the last century compared to the use of organic solvents, water is again becoming an increasingly important medium for organic reactions.[16] It is far from unusual to perform organometallic chemistry[17] or free-radical functionalization[18] of organic molecules in aqueous media. Also some mechanistic studies of the influence of water on the reactivity of organic molecules have been carried out.[19] However, iodination methods reported in water are very few.[12b,e,20] In our research water proved to be a suitable medium for the introduction of iodine into the studied substrates using iodine and a 30% aqueous solution of H_2O_2 as oxidizer in the presence of a catalytic amount of H_2SO_4. H_2O_2, widely accepted as a green oxidant,[21] was used to activate elemental iodine. H_2O_2 has several advantages over other oxidants: it is relatively cheap, relatively non-toxic, and breaks down readily to benign byproducts, thus avoiding environmental problems. However, its high activation potential ($E° = 1.77$ V) has to be overcome in order to successfully accomplish

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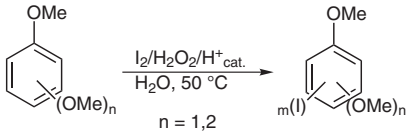
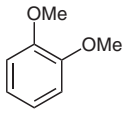
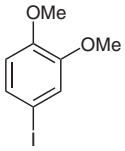
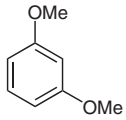
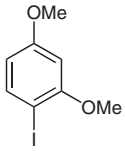
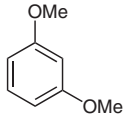
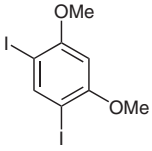
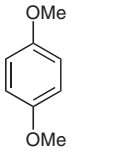
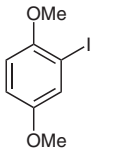
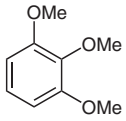
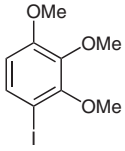
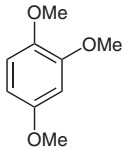
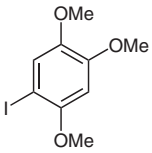
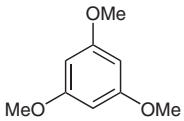
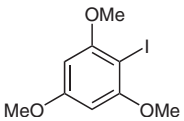
oxidation for less activated substrates. Therefore, an appropriate catalyst is of crucial importance for activation of H_2O_2 in such cases. In one of our previous studies a catalytic amount of H_2SO_4 was found to be a sufficient and efficient catalyst for the activation of H_2O_2 and for the further transformation of the iodinated products to ketones.[12d] It should also be noted that a high concentration of H_2O_2 can represent a certain safety risk during transportation, use, and storage, however, this can be easily avoided by the use of a 30% aqueous solution of H_2O_2[12a,12b,12d,12e] or by the use of a 'dry carrier' of hydrogen peroxide, e.g. a urea–H_2O_2 adduct or sodium percarbonate.[22]

Table 1 Iodination of Dimethoxy- and Trimethoxybenzenes in Water Using $I_2/H_2O_2/H^+$



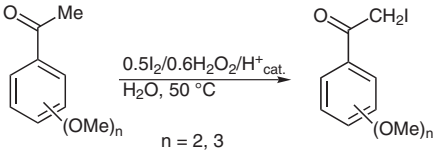
Entry	Substrate	Ratio[a]	Time (h)	Product	Conversion[b] (%)	Yield[c] (%)
1	 **1**	1:1:1	18	 **1a**	88	68[13]
2	 **2**	1:0.5:0.6	2	 **2a**	100	89
3	 **2**	1:1.5:1.5	15	 **2b**	100	85
4	 **3**	1:1:1	27	 **3a**	94	67[13]
5	 **4**	1: 1: 1	3	 **4a**	100	89
6	 **5**	1:0.5:0.6	4	 **5a**	95	83
7	 **6**	1:0.5:0.6	4	 **6a**	100	81

[a] Substrate/I_2/H_2O_2 ratio.
[b] Conversion of substrate determined from ^{1}H NMR spectra.
[c] Isolated pure product.

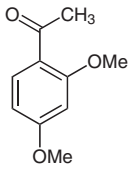
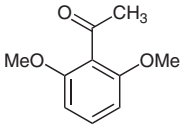
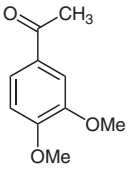
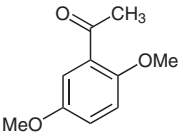
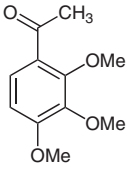
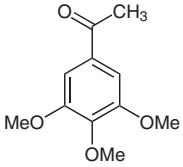
Among the methoxy-substituted benzene derivatives, 1,3-dimethoxybenzene (**2**) and 1,3,5-trimethoxybenzene (**6**), the most activated toward electrophilic substitution, were chosen as trial substrates.[12b] We found that 0.5 equivalent of iodine and 0.6 equivalent of H_2O_2 in the presence of a catalytic amount of H_2SO_4 were sufficient for the complete conversion to 1-iodo-2,4-dimethoxybenzene (**2a**) or 2-iodo-1,3,5-trimethoxy benzene (**6a**) at 50 °C after a few hours in aqueous medium. Encouraged by these results, we extended the method to 1,2-dimethoxybenzene (**1**), 1,4-dimethoxybenzene (**3**),[13] 1,2,3-trimethoxybenzene (**4**), and 1,2,4-trimethoxybenzene (**5**). Moreover, we attempted to achieve functionalization to diiodo derivatives by increasing the amount of reagent added. In the case of 1,2-dimethoxybenzene (**1**) and 1,4-dimethoxybenzene (**3**) the amount of reagent and the reaction time had to be increased to achieve comparable efficiency. With 0.5 equivalents of the reagent, the iodo-transformation was achieved with 51% yield of the iodinated product in the case of 1,2-dimethoxybenzene and even less in the case of 1,4-dimethoxybenzene. However, the yield was improved when one equivalent of the reagent was employed (Table 1, entries 1 and 4). The introduction of two iodine atoms was successfully achieved in the case of 1,3-dimethoxybenzene (Table 1, entry 3), while it failed for 1,2-dimethoxybenzene and 1,4-dimethoxybenzene, even with a huge excess of the added reagent. The reaction of 1,3-dimethoxybenzene and 1 equivalent of the reagent in water at 50 °C after 15 hours resulted in the formation of 1-iodo-2,4-dimethoxybenzene (**2a**) and 1,5-diiodo-2,4-dimethoxy benzene (**2b**) in a ratio of 1:1, while complete conversion to 1,5-diiodo-2,4-dimethoxybenzene (**2b**) was achieved with 1.5 equivalents of the reagent at 50 °C after 15 hours (Table 1, entry 3). In the case of trimethoxybenzenes water proved to be a suitable medium for the introduction of one iodine atom using the $I_2/H_2O_2/H^+$ catalyst system with high efficiency and atom economy (Table 1, entry 5–7). On the other hand, the introduction of two iodine atoms was found to be more difficult. Even with a large excess of the reagent complete conversion to diiodinated product was not achieved for any of the trimethoxy-substituted substrates studied in water. Still, 1,3,5-trimethoxybenzene is worth mentioning, the diiodinated product and monoiodinated product (**6a**) were present in a 88:12 ratio after a reaction time of 20 hours at 50 °C with 1.5 equivalents of reagent.

We then extended our research to dimethoxy- and trimethoxyacetophenones, where not only the suitability of water as a reaction medium for iodination with the $I_2/H_2O_2/H^+_{cat.}$ system, but also the regioselectivity of the transformation for selected substrates was of interest. Beside the aromatic ring, the α-alkyl position can also undergo electrophilic functionalization. In our previous study it was found that the regioselectivity in the functionalization of acetophenones could be efficiently regulated with the solvent used.[23] The iodinating system $I_2/H_2O_2/H^+$ in water showed α-alkyl regioselectivity for the dimethoxy- and trimethoxyacetophenones studied (Table 2). Moreover, 0.5 equivalents of the reagent proved to be sufficient for the introduction of one iodine atom into the α-alkyl position of the substrates under investigation, thus substantially contributing to the high atom economy of the reaction with regard to iodine. Attempts to introduce two iodine atoms into the molecule were successful in the case of 1-(1,6-dimethoxyphenyl)-1-ethanone (**8**) with one equiva-

Table 2 Iodination of Methoxy-Substituted Acetophenones in Water Using $I_2/H_2O_2/H^+$



7–12 **7a–12a**

Entry	Substrate	Time (h)	Conversion[a] (%)	Yield[b] (%)
1	 **7**	19	84	71
2	 **8**	18	72	54
3	 **9**	18	81	76
4	 **10**	18	86	76
5	 **11**	19	87	74
6	 **12**	18	59	48

[a] Conversion of substrate determined from ^{1}H NMR spectra.
[b] Isolated pure product.

lent of the reagent. However, conversion to 2,2-diiodo-1-(1,6-dimethoxyphenyl)-1-ethanone was not complete and 14% of monoiodinated product **8a** was still present in the reaction mixture after 18 hours at 50 °C in water. Moreover, difficulties during the purification process were encountered. After two consecutive column chromatographies (SiO_2, 1% EtOH in CH_2Cl_2), 10% of monoiodinated product **8a** was still present along with the major diiodinated product.

In conclusion, we feel that several aspects of the method presented for mild and efficient iodination of dimethoxy- and trimethoxybenzenes, as well as dimethoxy- and trimethoxy-substituted acetophenones, should be stressed. Firstly, water proved to be suitable for these transformations. Moreover, the reactivity of otherwise poorly reactive iodine was considerably enchanced by the use of a 30% aqueous solution of H_2O_2, widely recognized as a green oxidant, thus avoiding toxic waste as a side-product of the reaction. Only a catalytic amount of H_2SO_4 was needed to activate the oxidizing power of H_2O_2. In most cases a high atom efficiency for iodine was observed since only 0.5 equivalents of elemental iodine was needed for efficient transformation. Therefore, comparing the I_2/H_2O_2/H^+ system in water with other previously reported methods, which either employ large amounts of strong acids or heavy metal salts for enhancing the reactivity of iodine, we believe that the presented method makes a substantial contribution from the green chemistry point of view.

Iodine was purchased from Sigma Aldrich and used as received. A 30% aq solution of H_2O_2 was purchased from Merck; the precise content of active H_2O_2 was determined by the iodometric method; H_2O_2 was reacted with an acidic solution of a known, precisely weighed amount of KI, the amount of iodine released was calculated by titration with $Na_2S_2O_3$. Substrates were purchased from Sigma Aldrich and used as received, other chemicals (Na_2SO_4, $Na_2S_2O_3$, CH_2Cl_2) were purchased from Merck. Mps were determined on a Büchi apparatus. ^{1}H NMR spectra of crude reaction mixtures were recorded on a Varian EM 360L spectrometer at 60 MHz and spectra of purified products on a Varian INOVA 300 spectrometer at 300 MHz and ^{13}C NMR spectra on the same instrument at 76 MHz. Chemical shifts are reported in ppm from TMS as the internal standard. IR spectra were recorded on a Perkin–Elmer 1310 spectrometer. Standard KBr pellet procedures were used to obtain IR spectra of solids, while a film of neat material was used to obtain IR spectra of liquid products. MS were obtained on an Autospec Q instrument under EI conditions at 70 eV. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN analyzer.

General Procedure

Substrate (1 mmol) was added to H_2O (10 mL), followed by the addition of finely powdered I_2 (127 mg, 0.5 mmol; 254 mg, 1.0 mmol; 381 mg, 1.5 mmol; see Tables 1 and 2). After the mixture was stirred at 50 °C for a few minutes a 30% aq solution of H_2O_2 (containing 0.6 mmol, 20.4 mg or 1 mmol, 34.0 mg of active oxidant, see Tables 1 and 2) and a drop of 40% H_2SO_4 were added. The reaction mixture was vigorously stirred at 50 °C for various times (2–27 h, see Tables 1 and 2). When the reaction was complete the product was extracted with CH_2Cl_2 (20 mL), the organic phase was washed an aq solution of $Na_2S_2O_3$ (10%, 20 mL), H_2O (20 mL), dried over anhyd Na_2SO_4, and concentrated in vacuo. The crude reaction mixtures were analyzed by TLC and ^{1}H NMR spectroscopy. Pure samples of products were isolated by column chromatography (SiO_2; CH_2Cl_2 for **1a**–**6a**; 1% EtOH in CH_2Cl_2 for **7a**–**12a**), followed by crystallization in the case of solid products, and were identified on the basis of comparison of their spectroscopic data with the literature[5b,6b,23] or characterized by standard methods.

1-(2,5-Dimethoxyphenyl)-2-iodoethanone (10a)

Yield: 76%; white crystals (MeOH); mp 48.5–49.5 °C.

IR (KBr): 2995, 2940, 1660, 1490, 1460, 1405, 1325, 1280, 1250, 1220, 1100, 1040, 1010, 880, 840, 815, 730 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 4.51 (s, 2 H, CH_2I), 6.94 (d, *J* = 9.0, 1 H, Ar), 7.08 (dd, *J* = 9.0 Hz, 3.2 Hz, 1 H, Ar), 7.37 (d, *J* = 3.2 Hz, 1 H, Ar).

^{13}C (76 MHz, $CDCl_3$): δ = 9.5, 55.8, 56.1, 113.0, 114.6, 121.7, 124.2, 153.2, 153.5, 193.4.

MS (EI, 70 eV): *m/z* (%) = 306 (M^+, 55), 165 (100), 151 (7), 121 (18), 107 (10), 92 (12), 77 (20).

Anal. Calcd for $C_{10}H_{11}IO_3$: C, 39.24; H, 3.62. Found: C, 39.18; H, 3.62.

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