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A Comparison of Microwave-Accelerated and Conventionally Heated Iodination Reactions of Some Arenes and Heteroarenes, Using *ortho*-Periodic Acid as the Oxidant[†]

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Abstract: A fast and simple method for the oxidative iodination of some activated arenes and heteroarenes, either under *microwave irradiation* or by *conventional heating*, is reported, using diiodine and *ortho*-periodic acid as the oxidant. The reactions were carried out in hot 95% ethanol under a reflux condenser. For the microwave assisted reactions, the reaction times were always notably shortened, but the yields were nearly the same as those afforded by the conventional method.

Keywords: Oxidation, *ortho*-periodic acid as oxidant, oxidative iodination of activated arenes and heteroarenes, diiodine, microwave irradiation
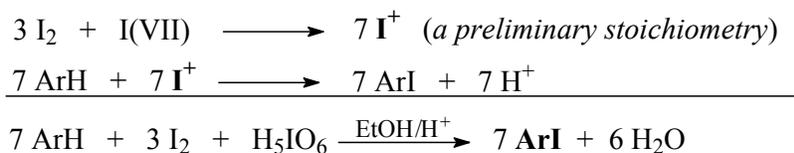
Introduction

The use of microwave irradiation to simplify and improve classic organic reactions has become a very popular technique, because it *sometimes* results in shorter reaction times, higher yields and cleaner reactions [1-4]. A number of reflux systems have been developed in an effort to use *solvents* in microwave assisted organic synthesis without the risk of explosion, since they work at atmospheric

pressure and flammable organic vapors cannot be released into the microwave cavity [1-4] – precisely with such a reflux system, with using also the focused *monomode* microwave irradiation, some microwave enhanced oxidative iodination reactions of a number of arylamines (*highly activated arenes*) have been carried out in our laboratory since 2003. In parallel, we have always carried out the same, or nearly the same, conventionally heated oxidative iodination reactions of the same arylamines in order to compare results, i.e. the reaction times and the yields of the purified iodinated products afforded by the two different experimental techniques. Our earlier microwave-accelerated iodination reactions were carried out under a reflux condenser using either boiling CHCl$_3$ (b.p. 61 °C) as the solvent of choice and a urea-hydrogen peroxide addition compound (UHP) as the oxidant [5], or boiling CH$_2$Cl$_2$ (b.p. 42 °C) as the solvent of choice and *ortho*-periodic acid (H$_5$IO$_6$) as the oxidant [6]. In the both cases, the microwave assisted oxidative iodination reactions of several arylamines afforded nearly the same yields of the purified iodinated products as those heated conventionally, but the reactions were always *notably accelerated* by microwave irradiation; for more details see our former papers [5, 6]. However, we could hardly iodinate effectively some *less activated* arenes under the aforesaid experimental conditions. The aim of this work is thus the extension of the scope of our former iodination methods to other substrates, i.e. to a number of activated arenes or heteroarenes (Table 1), all less active than arylamines in their electrophilic substitution reactions.

It is necessary to strongly emphasize that our former paper [5], published in 2002, was the first one in the literature to report that *oxidative iodination of arenes* (*viz.* highly activated arylamines) was notably accelerated by microwave irradiation. In 2003 Italian chemists [7] reported the direct microwave-assisted iodination of several pyrimidinones and pyrimidine nucleosides mixed with *N*-iodosuccinimide and DMF to give the corresponding 5-iodo derivatives in high yields; the samples were irradiated for 3 minutes in a microwave oven at 200 W, whereas the same yields were obtained under thermal conditions for 360 minutes at 70 °C. Application of this microwave-assisted reaction to polymer-bound pyrimidinones was also investigated there. In 2004 Bogdal and co-workers [8] reported the effective application of microwave irradiation to the oxidative chlorination, bromination, and ***iodination*** of carbazole and several aromatic compounds, in the presence of hydrogen peroxide - hydrohalic acids (water solutions of HCl, HBr or HI) system.

Results and Discussion

It is known from the literature [9, 10] that the oxidative iodination reactions of aromatics are very often notably accelerated by acid catalysts (e.g. concd H$_2$SO$_4$ or aq. HCl). *ortho*-Periodic acid, H$_5$IO$_6$, exhibits some definite acidic properties in aqueous solutions [11], hence we changed the previously used toxic chlorinated solvents [5, 6] for a commercial 95% *ethanol* (bp 78 °C) in which H$_5$IO$_6$ alone would satisfactorily be dissociated to H$_3$O$^+$ + H$_4$IO$_6^-$ to facilitate the oxidation of diiodine by H$_5$IO$_6$, and to form some **I**$^+$ species, capable of effectively iodinating a number of activated arenes or heteroarenes, ArH, shown in Table 1:

$$3\ I_2\ +\ I(VII)\ \longrightarrow\ 7\ \mathbf{I}^+\quad (\textit{a preliminary stoichiometry})$$

$$\underline{7\ ArH\ +\ 7\ \mathbf{I}^+\ \longrightarrow\ 7\ ArI\ +\ 7\ H^+}$$

$$7\ ArH\ +\ 3\ I_2\ +\ H_5IO_6\ \xrightarrow{\ EtOH/H^+\ }\ 7\ \mathbf{ArI}\ +\ 6\ H_2O$$

Thus, H_5IO_6 and finely powdered diiodine were suspended, with stirring, in a suitable volume of 95% ethanol. Next, a chosen arene or heteroarene, ArH, was added, and such composite reaction mixtures were further reacted *in two different ways* as follows:

a) *by conventional heating*: the vigorously stirred reaction mixtures were heated under a reflux condenser at 60 °C for 30-60 minutes (Table 1);

b) *by focused monomode microwave irradiation* under an externally attached reflux condenser and with stirring: the reaction mixtures were placed into the microwave cavity and were then irradiated for 1-10 minutes (Table 1); an appropriate power output was used to secure mild, uninterrupted reflux of the solvent.

After completing the reactions (which were monitored by TLC), the cooled reaction mixtures were poured into a vigorously stirred excess of aq. Na_2SO_3 solution (*a reductant* used to destroy any unreacted diiodine and all possible oxidized species). The liquid suspensions were extracted with $CHCl_3$, the organic layers were dried over anhydrous $MgSO_4$, filtered, the solvent was distilled off and the oily residues were fractionated under vacuum to obtain the purified liquid products. The precipitated crude solid products were collected by filtration, washed well with cold water, air-dried in the dark, and recrystallized from appropriate organic solvents to give the purified solid products. The purities and homogeneities of the purified products were first checked by TLC, then their ^{1}H- and ^{13}C-NMR spectra (not shown here) were compared with those of authentic specimens [12]. Fairly sharp melting points (uncorrected) were very close to those reported in the literature [13], as well as correct microanalyses (I ± 0.4%) which further confirmed the chemical structures of the purified iodinated products.

Only the purified 4-iodotoluene obtained from toluene, the 4-iodo-1,2-dimethylbenzene obtained from *o*-xylene, and the 2-iodoimidazole obtained from imidazole were admixed with ca. 5-8% of their isomeric monoiodinated side products, as revealed by TLC and the NMR spectra; these byproducts could not be removed by simple repeated recrystallizations or by repeated fractionations under vacuum. Such isomeric mixtures can be resolved only by chromatographic techniques or by tedious fractional crystallizations from appropriate solvents [14].

From Table 1 it is seen that the microwave assisted iodination reactions afforded 44-91% yields, whereas conventionally heated ones also gave 41-92% yields, but the former ones were always *notably accelerated* as compared with the "classical" ones (Table 1), hence it is worthwhile to apply microwaves for the enhancement of some oxidative aromatic iodination reactions. However, we have established that for the iodination reactions carried out *in very strongly polar and acidic media,* e.g. in anhydrous $AcOH/Ac_2O/$concd H_2SO_4 solutions [10] or in 90% (v/v) sulfuric acid [15], the strict temperature control during the irradiation by microwaves is hardly possible, due to the easy overheating of such reaction mixtures, which very often ends up in overboiling.

Experimental

General

The melting points for the freshly recrystallized and microanalyzed (%I) iodinated products are uncorrected (Table 1). All reagents were commercial (Aldrich), only 95% ethanol was produced in

Poland. Elemental microanalyses (%I) were performed at the Institute of Organic Chemistry, Polish Academy of Sciences in Warsaw, while ^{1}H- and ^{13}C-NMR spectra (not given here) were recorded at r.t. with a Brucker AVANCE DMX 400 MHz spectrometr, and next they were compared with the same spectra of authentic specimens [12]. Our microwave experiments were performed with a microwave oven (at 2450 MHz) purchased from "Plazmatronika" (Wroclaw, Poland), described in detail in our former papers [5, 6]; Our present iodination experiments were carried out with a focused monomode MW irradiation.

Table 1. Pure iodinated products prepared. The literature m.p. or b.p. are taken from Ref. 13.

Product	Conventional method			Microwave irradiation		
	Time (min)	Yield (%)	M.p./Lit. M.p. (°C)	Time (min)	Yield (%)	M.p./Lit. M.p. (°C)
4-iodoanisole	30	89	50-51/51-52	5	86	50-51/51-52
4-iodophenetole	30	72	29-30/29-30	7	71	30-31/29-30
Iodomesitylene	30	89	30-31/30-31	7	85	30-31/30-31
4-iodoacetanilide	30	86	183-184/182-184	5	82	182-184/182-184
4-iodo-3-methylanisole	30	72	44-45/44-45	5	71	43-44/44-45
4-iodo-1-methoxynaphthalene	30	84	53-55/54-56	5	83	53-55/54-56
1-iodo-2-methoxynaphthalene	30	91	87-88/88-89	5	91	89-90/88-89
4-iodo-1,3-dimethoxynaphthalene	30	92	40-41/40-41	1	91	40-41/40-41
4-iodotoluene[a]	45	43	bp 101-103(15)/ bp 210-211(760)	10	44	bp 103-104(15)/ bp 210-211(760)
4-iodo-1,2-dimethylbenzene[a]	45	48	bp 139-141(15)/ bp 229-230(760)	10	46	bp 139-142(15)/ bp 229-230(760)
4-iodo-1,3-dimethylbenzene	45	75	bp 134-135(15)/ bp 230-231(760)	10	75	bp 134-136(15)/ bp 230-231(760)
3-iodo-1,4-dimethylbenzene	45	41	bp 139-142(15)/ bp 228-232(760)	10	42	bp 140-143(15)/ bp 228-232(760)
4-iodo-1,2-ethylenedioxybenzene	45	73	bp 127-130(15)/ bp 242-243(760)	7	70	bp 129-131(15)/ bp 242-243(760)
5-iodouracil	45	82	277-278/276-277	10	81	278-279/276-277
5-iodo-6-methylouracil	45	80	262-264/263-265	10	80	262-264/263-265
4-iodopyrazole	30	75	112-113/112-113	7	77	112-113/112-113
2-iodoimidazole[a]	45	72	191-192/192-194	10	72	191-192/192-194
2-iodothiophene	30	69	bp 180-182(760)/ bp 180-182(760)	5	68	bp 179-181(760)/ bp 180-182(760)
2,5-diiodothiophene	60	62	40-41/40-41	10	64	40-41/40-41

[a] The recrystallized compounds were admixed by ca. 5-8% of isomeric monoiodinated side products (TLC, NMR).

Conventionally Heated Iodination Reactions

H_5IO_6 (1.43 g, 6.25 mmol; 25% excess), finely powdered I_2 (3.81 g, 15.0 mmol; 0% excess), and then an appropriate *arene* (35.0 mmol; 0% excess) [for the diiodination of *thiophene* 17.5 mmol, 0% excess] were suspended in 95% ethanol (15 mL). The reaction mixtures were stirred and heated under a reflux condenser at ca. 60 °C for 30-60 min (Table 1). The cooled reaction mixtures were quenched by pouring them into stirred ice-water (100 g) containing prior dissolved Na_2SO_3 (5 g). The oily crude iodinated products were extracted with $CHCl_3$ (3 x 20 mL), the collected extracts were dried over anh. $MgSO_4$, filtered, the solvent was distilled off, and the oily residues were fractioned under vacuum to give the purified liquid products (Table 1). The solid crude products were collected by filtration, washed well with cold water, dried preliminarily by the suction, and next air-dried in the dark. They were recrystallized from appropriate organic solvents to give the purified solid products (Table 1).

Microwave-Accelerated Iodination Reactions

The same as above amounts of H_5IO_6, I_2, and the appropriate *arene* were suspended in 95% ethanol (25 mL). The reaction mixtures were put into the microwave cavity, and the magnetic stirrer was switched on. An appropriate power output was applied (50%, 500 W) to secure a slight, uninterrupted boil of the solvent under a reflux condenser attached outside. After a definite time (1-10 min, see the Table 1), the reaction mixtures were cooled to r.t., and then they were poured, as above, into stirred ice-water (100 g) containing Na_2SO_3 (5 g). The following workups and purification of the oily or solid crude products were quite the same as above. For the final results thus obtained see the Table 1.

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11. *ortho*-Periodic acid is a weak acid ($pK^1 = 1.64$, $pK^2 = 2.3 \times 10^{-2}$), comparable in strength to *meta*-phosphoric acid or oxalic acid. It is a strong oxidant, somewhat stronger than HIO_3. In aqueous solutions of H_5IO_6 (pH = 1-7), it exists as an equilibrium mixture between the free acid and various ions, mostly monoanionic species. Suzuki and co-workers (*vide infra*) found the combination $I_2 + H_5IO_6$ (*the Suzuki reagent*) to be an efficient iodinating agent for a series of polyalkylated benzenes, as well as some polycyclic and heterocyclic aromatic compounds. The reactions were mostly carried out at 60-90 °C in acetic acid – water with a little concd sulfuric acid. For more details see: a) Suzuki, H.; Nakamura, K.; Goto, R. The direct iodination of polyalkylbenzenes bearing bulky groups. *Bull. Chem. Soc. Jpn*. **1966**, *39*, 128-131; b) Fatiadi, A. J. New Applications of Periodic Acid and Periodates in Organic and Bio–Organic Chemistry. *Synthesis* **1974**, 229-272. See pp. 230 and 242-243; c) Fatiadi, A. J. In *Synthetic Reagents*, Vol. 4; Pizey, J. S., Ed.; Halsted Press – Wiley: New York, 1981. See pp. 184-185.

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Sample Availability: Available from the authors.