Comparative Study of the Reactivity of Iodinating Agents in Solution and Solid Phase

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Abstract—The results of reactions of a series of aromatic substrates with iodine, iodine(I) chloride, and *N*-iodosuccinimide in solution and solid phase were compared for the first time. In all cases, the general relations holding in the iodination process were similar. Iodine(I) chloride was found to chlorinate anthracene. A high efficiency of solid-phase iodination of β-diketones was demonstrated using dibenzoylmethane as an example.

Aromatic iodides are indispensable building blocks in organic synthesis, and some their derivatives are important drugs and diagnostics [1]. A promising line in modern organic synthesis includes carrying out chemical reactions in a solid phase without a solvent, i.e., so-called solvent-free processes. However, examples of such processes in the field of electrophilic aromatic iodination are almost unknown. Only recently, some information has been published on the solid-phase iodination of aromatic compounds with tetramethylammonium dichloroiodate ($Me_4N^+ ICl_2^-$) [2] and iodine in the presence of bismuth(III) nitrate [3]. Unfortunately, there are no data on general relations holding in the solid-phase iodination and on the behavior under these conditions of iodinating agents commonly used in liquid-phase processes.

The goal of the present work was to elucidate general relations holding in solid-phase iodination at room temperature and under mechanochemical activation with such iodinating agents as molecular iodine, iodine(I) chloride, and *N*-iodosuccinimide (NIS). As substrates we used durene (**I**), biphenyl (**II**), phenol (**III**), carbazole (**IV**), and anthracene (**V**), i.e., compounds for which the results of liquid-phase iodination with the same reagents have been well documented. The results of our comparative experiments are given in table.

Molecular iodine turned out to be inactive with respect to all the examined substrates in the solid phase. Analogous behavior in the absence of an oxidant is typical of reactions in solution. On the other hand, it is well known that iodine is capable of reacting with highly nucleophilic phenoxides (see, e.g., [4]). In fact, sodium phenoxide effectively reacted with iodine in the solid phase to afford 2,4,6-triiodophenol (**IIIa**) in nearly quantitative yield. More active iodine(I) chloride vigorously reacted with durene (**I**) in the absence of a solvent. The reaction was exothermic, so that the mixture melted, and gaseous HCl and ICl evolved. The process terminated in 15–20 min, and subsequent grinding of the mixture in a mortar did not lead to an appreciable change in its composition. However, the conversion of initial arene **I** was incomplete even when the ICl:**I** ratio was 2:1, and the yield of iododurene (**Ia**) did not exceed 40%. We have found that preliminary mixing ICl with silica gel and subsequent contact of the resulting mixture with durene (**I**) ensures smooth iodination and high conversion of the substrate and prevents loss of ICl. In this way, iododurene (**Ia**) was isolated in 88% yield.

The reaction of carbazole (**IV**) with ICl both in the presence and in the absence of silica gel was accompanied by oxidation to produce an inseparable mixture of products among which 3-iodo- and 3,6-diiodocarbazoles were detected by thin-layer chromatography.

Solid-phase reaction of anthracene (**V**) with ICl attracted a specific interest, taking into account that iodine(I) chloride in organic solvents or sulfuric acid acts as chlorinating rather than iodinating agent [5, 6]. When anthracene (**V**) was brought into a contact with ICl, the latter instantaneously decomposed with evolution of iodine vapor, while the substrate was converted into a mixture of 9-chloro- and 9,10-dichloroanthracenes **Va** and **Vb** (TLC data). The same result was

Iodination of arenes **I–VII** with ICl and NIS in solution and under solvent-free conditions

Substrate/reagent	Solvent	Time, h	Tempera-ture, °C	Substrate–reagent molar ratio	Product, yield, %
Phenol (**III**)/I$_2$, NaOH	No solvent	0.5	20	1:3.6	2,4,6-Triiodophenol (**IIIa**), 70
Durene (**I**)/ICl	Aqueous H$_2$SO$_4$, 10 vol % [16]	2.5	100	10:10	Iododurene (**Ia**), 76
Durene (**I**)/ICl	No solvent	1	20	1:2	Iododurene (**Ia**), 40
Durene (**I**)/ICl[a]	" "	1	20	1:1.4	Iododurene (**Ia**), 88
Carbazole (**IV**)/ICl	Acetonitrile [11]	1.5	20	1:1.5	3-Iodocarbazole (**IVa**), 63
Carbazole (**IV**)/ICl	No solvent	0.5	20	1:2	Mixture of 3- and 3,6-diiodo-carbazoles; strong tarring
Anthracene (**V**)/ICl	Acetonitrile [6]	2.5	20	1.26:1	9-Chloroanthracene (**Va**), 66.8; 9,10-dichloroanthracene (**Vb**), 4.52
Anthracene (**V**)/ICl	Aqueous H$_2$SO$_4$, 10 vol % [5]	3	100	10:40	9,10-Dichloroanthracene (**Vb**), 37
Anthracene (**V**)/ICl	No solvent	0.5	20	1:4	9,10-Dichloroanthracene (**Vb**), 55
Phenol (**III**)/ NIS	EtOH–H$_2$SO$_4$	0.5	20	1:3	2,4,6-Triiodophenol (**IIIa**), 64
Phenol (**III**)/ NIS	No solvent	0.5	20	1:3	2,4,6-Triiodophenol (**IIIa**), 75
Durene (**I**)/NIS	AcOH–H$_2$SO$_4$ [9]	0.5	20	1:1	Iododurene (**Ia**), 76
Durene (**I**)/NIS–H$_2$SO$_4$	No solvent	0.5	20	1:1.2	Iododurene (**Ia**), 75
Biphenyl (**II**)/NIS	AcOH/H$_2$SO$_4$ [9]	3	20	1:2	4,4'-Diiodobiphenyl (**IIa**), 75
Biphenyl (**II**)/NIS–H$_2$SO$_4$	No solvent	1.5	20	1:1.2	4-Iodobiphenyl (**IIb**), 65
Carbazole (**IV**)/NIS	CHCl$_3$–AcOH, 3:1 [10]	2	25	1:2	6-Iodocarbazole (**IVa**), 35; 3,6-diiodocarbazole (**IVb**), 65
Carbazole (**IV**)/NIS–H$_2$SO$_4$	No solvent	0.5	20	1:4	Mixture of 3- and 3,6-diiodo-carbazoles; strong tarring
Biphenyl (**II**)/NIS–TsOH	" "	2	20	1:1.2	4-Iodobiphenyl (**IIb**), 60
Naphthalene (**VI**)/NIS–TsOH	" "	2	20	1:1.1	1-Iodonaphthalene (**VIa**), 50
Acetanilide (**VII**)/NIS–TsOH	" "	0.5	20	1:1.2	*p*-Iodoacetanilide (**VIIa**), 93

[a] In the presence of silica gel.

obtained in the presence of silica gel. In the reaction of **V** with 4 equiv of ICl we succeeded in isolating compound **Vb** in 55% yield (see table). Thus iodine(I) chloride acts as chlorinating agent with respect to anthracene (**V**) both in solution and in solid phase, which is important for understanding the mechanism of this reaction.

N-Iodosuccinimide (NIS) has long been known as iodinating agent. It is effective toward a wide spectrum of substrates, from phenols and anilines to nitrobenzene which is deactivated to electrophilic substitution. It is also known that NIS exhibits the maximal activity in strongly acidic medium, e.g., in trifluoromethane-sulfonic acid [7] and sulfuric acid [8]. Phenol reacts with NIS under solvent-free conditions to give triiodo

derivative **IIIa** (yield 75–80%). For comparison, we also examined the reaction of phenol (**III**) with *N*-bromosuccinimide (NBS) under analogous conditions. The reaction with NBS was much more vigorous, and bromine vapor instantaneously evolved. To make the process smoother, a required amount of NBS was added in three portions; 2,4,6-tribromo-phenol was isolated in 85–90% yield.

N-Iodosuccinimide turned out to be inactive toward substrates **I**, **II**, **IV**, and **V** in the solid phase, and the initial compounds were recovered from the reaction mixtures. However, addition of a catalytic amount of sulfuric acid strongly activated the iodinating agent. By reactions of durene (**I**) and biphenyl (**II**) with NIS preliminarily ground with three drops of H$_2$SO$_4$ we

obtained 75% of iododurene (**Ia**) and 65% of 4-iodo-biphenyl, respectively. Under analogous conditions, anthracene was slowly oxidized to anthraquinone.

Despite acid activation, the reactivity of *N*-iodo-succinimide under solvent-free condition was lower than in solution. Nitrobenzene and *p*-nitrotoluene remained unchanged upon grinding with NIS in the presence of H$_2$SO$_4$, whereas nitroarenes were success-fully iodinated with NIS in sulfuric acid solution at room temperature [8, 9]. In addition, the system NIS–H$_2$SO$_4$ showed a low selectivity with respect to carba-zole (**IV**). Treatment of carbazole with an equimolar amount of NIS afforded a mixture of 3-iodo- and 3,6-diiodocarbazoles, the substrate conversion was not complete (TLC), and the reaction was accompanied by tarring. It should be noted that iodination of carbazole in solution is often characterized by low selectivity as well [10, 11].

We were the first to demonstrate that *N*-iodo-succinimide can be activated by *p*-toluenesulfonic acid (molar ratio 1:1) under solvent-free conditions. In doing so, we succeeded in reducing side tar formation to an appreciable extent, while the efficiency of the iodinating system remained unchanged. The other relations also did not change: anthracene underwent slow oxidation rather than iodination, biphenyl was smoothly converted into 4-iodobiphenyl, and carbazole gave rise to a mixture of iodo derivatives which were difficult to separate (see table).

The solvent-free iodination of naphthalene (**VI**) with NIS in the presence of *p*-toluenesulfonic acid gave 50% of 1-iodonaphthalene (**VIa**); this reaction cannot be effected under catalysis by sulfuric acid. The reaction was highly selective: according to the ^{13}C NMR data, the ratio of 1- and 2-iodonaphthalenes was about 95:5. It should be noted that spontaneous libera-tion of iodine was observed while recording the NMR spectra of **VIa** in CDCl$_3$ and CHCl$_3$. Under analogous conditions, the iodination of acetanilide (**VII**) gave 93% of 4-iodoacetanilide (**VIIa**) with high *para* selectivity.

N-Iodosuccinimide was highly effective in the monoiodination of dibenzoylmethane (**VIII**) in the absence of acid catalyst. Grinding of compound **VIII** with NIS over a period of 10 min resulted in almost complete conversion of the substrate, and pure diben-zoyl(iodo)methane (**VIIIa**) was isolated in 97% yield. This reaction is the first example of solid-phase iodination of β-diketones, and it clearly demonstrates synthetic, ecological, and economic advantages of the

proposed procedure. Iodide **VIIIa** prepared by iodo-debromination of the corresponding bromo-β-diketone [12] or by electrochemical iodination [13] spontane-ously loses iodine at an appreciable rate when contacts with a number of solvents (acetone, benzene, chloro-form, methylene chloride). The solid-phase procedure allows us to minimize operations in solvents and isolate pure product **VIIIa**.
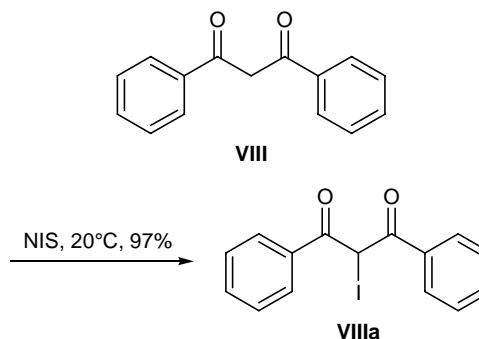
The results of our study led us to conclude that general relations holding in the iodination with I$_2$, ICl, and NIS in solution are also typical of reactions performed under solvent-free conditions. These are the following: (1) molecular iodine is capable of iodinat-ing only phenoxide and is inactive toward arenes; (2) ICl reacts with anthracene to give chloro rather than iodo derivative; and (3) the iodinating power of NIS increases in the presence of strong acids. More-over, in some cases the solid-phase iodination proce-dure is obviously more advantageous due to its simplicity, mild conditions, high reaction rate, and minimization of operations involving organic solvents.

EXPERIMENTAL

The progress of reactions was monitored, and the purity of products was checked, by TLC on Sorbfil PTsKh-P-A-UF and Silufol UV-254 plates; spots were visualized under UV light; the following solvents were used as eluents: hexane (anthracene, durene), benzene (biphenyl, *p*-nitrotoluene, phenol, dibenzoylmethane), and hexane–diethyl ether (2:1) (carbazole).

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avante-300 spectrometer (300 MHz) using HMDS as internal reference and CDCl$_3$ as solvent. The melting points were determined on a Boetius melting point apparatus.

The products were identified by comparing their analytical and physical parameters with those of authentic samples (no depression of the melting points was observed on mixing).

Iodine(I) chloride was prepared by the procedure described in [14]; it was purified and analyzed according to [15]. Iodine of ultrapure grade, sulfuric and acetic acids of analytical grade, *p*-toluenesulfonic acid monohydrate of pure grade, *N*-bromosuccinimide of chemically pure grade, and Silicagel L (40/100 μm) were used. *N*-Iodosuccinimide was prepared by the procedure reported in [5].

General procedure for reaction of arenes with ICl. Iodination of durene (I) in the presence of silica gel. Preliminarily frozen iodine(I) chloride, 0.5 g (2.8 mmol), and silica gel, 2.5 g, were thoroughly ground in an agate mortar until a uniform mixture was obtained. Durene, 0.27 g (2 mmol), was then added, and the mixture was ground for 45 min, left to stand for 15 min, and dissolved in acetonitrile. Silica gel was filtered off, the filtrate was poured into 10% aqueous Na_2SO_3, and the precipitate was filtered off, dried in air, and recrystallized from glacial acetic acid. Yield of iododurene 0.45 g (88%), mp 77–78°C; published data [16]: mp 76–78°C.

General procedure for reaction of arenes with *N*-iodosuccinimide. Iodination of biphenyl (II) with NIS–H_2SO_4. Three drops of sulfuric acid were added to 0.5 g (2.2 mmol) of NIS, the mixture was ground in an agate mortar until a uniform material was obtained, 0.3 g (2 mmol) of biphenyl was added, and the mixture was ground for 10 min and was left to stand for 1.5 h. The mixture was treated with a 10% aqueous solution of sodium sulfite, and the precipitate was filtered off, dried in air, and recrystallized from ethanol. Yield of 4-iodobiphenyl 0.36 g (65%), colorless crystals, mp 112–113°C [5].

Iodination of phenol (III) with iodine in the presence of sodium hydroxide. A mixture of 0.09 g (1 mmol) of phenol and 0.5 g (12.5 mmol) of NaOH was ground in an agate mortar. Silica gel, 0.2 g, and iodine, 0.91 g (3.6 mmol), were added to the resulting colorless crystalline material, and the mixture was ground for 30 min and treated with dilute hydrochloric acid. The precipitate was filtered off and dried. The organic products were dissolved in benzene, silica gel was filtered off, and the filtrate was evaporated under reduced pressure. The residue was subjected to column chromatography using benzene as eluent to isolate 0.326 g (70%) of 2,4,6-triiodophenol with mp 156–157°C [17].

Iodination of acetanilide (VII) with *N*-iodosuccinimide in the presence of *p*-toluenesulfonic acid. A mixture of 0.27 g (1.2 mmol) of NIS and 0.23 g (1.2 mmol) of *p*-toluenesulfonic acid was ground in an agate mortar until a uniform material was obtained, 0.14 g (1 mmol) of acetanilide was added, and the mixture was stirred for about 5 min. During this procedure the mixture melted and then crystallized in 30 min. The mixture was treated with 25 ml of a 10% solution of Na_2SO_3, and the precipitate was filtered off, washed with water on a filter, and dried. Yield of 4-iodoacetanilide 0.24 g (93%), colorless crystals, mp 179–180°C [17]. ^{1}H NMR spectrum, δ, ppm: 2.163 s (3H, $COCH_3$), 7.28 d (2H, H_{arom}, $J = 9$ Hz), 7.6 d (2H, H_{arom}, $J = 8.7$ Hz). ^{13}C NMR spectrum, $δ_C$, ppm: 26.24, 87.15, 122.2, 136.52, 138.02, 169.3.

Iodination of naphthalene (VI) with *N*-iodosuccinimide in the presence of *p*-toluenesulfonic acid. A mixture of 0.5 g (2.2 mmol) of NIS and 0.42 g (2.2 mmol) of *p*-toluenesulfonic acid was ground in an agate mortar until a uniform material was obtained, 0.26 g (2 mmol) of naphthalene was added, and the mixture was ground for 10 min. The mixture was kept for 2 h, treated with 15 ml of a 10% solution of Na_2SO_3, and extracted with methylene chloride. The extract was dried over $MgSO_4$ and evaporated under reduced pressure to obtain 0.3 g of an oily substance which was subjected to column chromatography using hexane as eluent. Yield of **VIa** 0.25 g (50%), colorless oily substance. ^{13}C NMR spectrum, $δ_C$, ppm: 99.8, 126, 126.6, 126.9. 127.9, 128.1, 128.7, 129.6, 132.3, 137.6. The spectrum also contained weak signals at $δ_C$ 92.5, 126.65, 129.86, 135.02, and 136.92 ppm, belonging to 2-iodonaphthalene (~5%).

Iodination of dibenzoylmethane (VIII) with *N*-iodosuccinimide. A mixture of 0.22 g (1 mmol) of dibenzoylmethane and 0.27 g (1.2 mmol) of NIS was ground in an agate mortar for 10 min. The mixture was then dissolved in 4 ml of acetonitrile, the solution was poured into water, and the precipitate was filtered off, washed with water, and dried in a desiccator. Yield 0.34 g (97%) of dibenzoyl(iodo)methane, light yellow crystals, mp 104–105.5°C; published data [12]: mp 100°C. ^{13}C NMR spectrum, $δ_C$, ppm: 34.4, 129.6, 129.7, 133.6, 134.6, 190.5. ^{1}H NMR spectrum, δ, ppm: 6.89 s (1H, CH), 7.96 – 7.39 m (10H, H_{arom}).

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