Solvent-free iodination of organic molecules using the I$_2$/urea–H$_2$O$_2$ reagent system

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

Introduction of iodine under solvent-free conditions into several aromatic compounds activated toward electrophilic functionalisation was found to proceed efficiently using elemental iodine in the presence of a solid oxidiser, the urea–H$_2$O$_2$ (UHP) adduct. Two types of iodo-functionalisation through an electrophilic process were observed: iodination of an aromatic ring, and side-chain iodo-functionalisation in the case of arylalkyl ketones. Two reaction routes were established based on the required substrate : iodine : oxidiser ratio for the most efficient iodo-transformation, and the role of UHP was elucidated in each route. The first, requiring a 1 : 0.5 : 0.6 stoichiometric ratio of substrate to iodine to UHP, followed the atom economy concept in regard to iodine and was valid in the case of aniline (**1a**), 4-t-Bu-phenol (**3**), 1,2-dimethoxy benzene (**5a**), 1,3-dimethoxy benzene (**5b**), 1,2,3-trimethoxy benzene (**7a**), 1,2,4-trimethoxy benzene (**7b**), 1,3,5-trimethoxy benzene (**7c**), 1-indanone (**11a**) and 1-tetralone (**11b**). The second reaction route, where a 1 : 1 : 1 stoichiometric ratio of substrate : I$_2$: UHP was needed for efficient iodination, was suitable for side-chain iodo-functionalisations of acetophenone (**1c**) and methoxy-substituted acetophenones. Moreover, addition of iodine to 1-octene (**13a**) and some phenylacetylenic derivatives (**15a**, **15b**) was found to proceed efficiently without the presence of any oxidiser and solvent at room temperature.

Introduction

Due to the importance of iodo-substituted organic compounds as synthons or valuable precursors in organic synthesis,[1] in addition to their use as radioactively-labelled markers in medical diagnosis,[2] the introduction of iodine into organic molecules has received significant attention among the scientific community. Since molecular iodine itself is poorly reactive, substantial efforts have been invested in the development of efficient, selective and mild methods for direct introduction of iodine into organic compounds. Numerous diverse procedures using iodonium donating agents have been devised over the years.[3] Beside the use of volatile organic solvents as reaction media, many of them employ harsh conditions, such as the extensive use of strong acids or the use of heavy metal salts or their oxides as activators of iodine,[4] which require special safety precautions in experimental handling and pose serious concerns regarding environmental and health issues. Contrary to traditional thinking on the necessity of an appropriate organic solvent for performing a reaction, in keeping with a green chemistry approach, which emerged a decade ago as a response to continuously growing concerns for sustainable development, the best solvent is regarded to be 'no solvent at all'.[5] Thus, solvent-free reactions are garnering increased attention in recent years.[6] Their advantages over conventional methods may, in many cases, be attributed to enhanced efficiency and selectivity, cleaner products, milder reaction conditions, lower reaction times, simplified procedures and hence the reduction of pollution. However, iodination under solventless conditions has not been

extensively studied.[7] Hydrogen peroxide, widely accepted as a green oxidant, was used to activate and/or regenerate elemental iodine. Having several advantageous properties compared to other oxidants, the most notable being the formation of water as a benign by-product of oxidation, resulted in its comprehensive application in several oxidation systems.[8] The solid urea–H$_2$O$_2$ adduct (NH$_2$CONH$_2$–H$_2$O$_2$, UHP) and sodium percarbonate (Na$_2$CO$_3$–1.5H$_2$O$_2$, SPC) are regarded as 'dry carriers' and safer alternatives to hazardous, unstable concentrated liquid hydrogen peroxide.[9] Moreover, their easy handling, stability at room temperature and ability to release oxidative species in a controlled manner make them desirable oxidisers. Both already proved to be efficient for oxidative iodination of various organic compounds in an EtOAc–AcOH mixture under highly acidic conditions and in CHCl$_3$ under microwave irradiation.[10] In our on-going efforts to achieve environmentally friendlier halogenation procedures,[11] we investigated iodination using iodine in the presence of both the above mentioned solid forms of hydrogen peroxide (UHP and SPC) without the use of a solvent for carrying out iodo-transformation, and compared the results with previously performed studies on iodination using iodine and a 30% aqueous solution of H$_2$O$_2$ as oxidiser in water.[11h,11i] In response to ever-increasing demands for ecologically more acceptable procedures, our research was aimed at solvent-free reaction conditions for iodine introduction. Methoxy-substituted aromatic derivatives were chosen as plausible substrates for investigating the course of transformation because of the known fact that the activated aromatic ring in the substituted molecules of the chosen substrates can readily undergo ion-radical formation with various oxidising agents. Moreover, the acetophenone moiety attracted our attention for studying the regioselectivity of the transformation. In regard to the studied substrates, the iodination process was

[a]Laboratory for Organic and Bioorganic Chemistry, 'Jožef Stefan Institute', Jamova 39, 1000, Ljubljana, Slovenia. E-mail: stojan.stavber@ijs.si
[b]Department of Chemistry at the Faculty for Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, 1000, Ljubljana, Slovenia

expected to proceed potentially through 3 different intermediates, while 2 types of iodo-functionalisation were anticipated, namely aromatic ring iodo-functionalisation and side-chain functionalisation in the case of arylalkyl ketones (Scheme 1). In accordance with our previous experience, an ionic mechanism with formation of a σ-complex in the intermediate stage was expected to be differentiated from a SET process with ion-radical formation on the basis of the amount of reagent used.[11h]
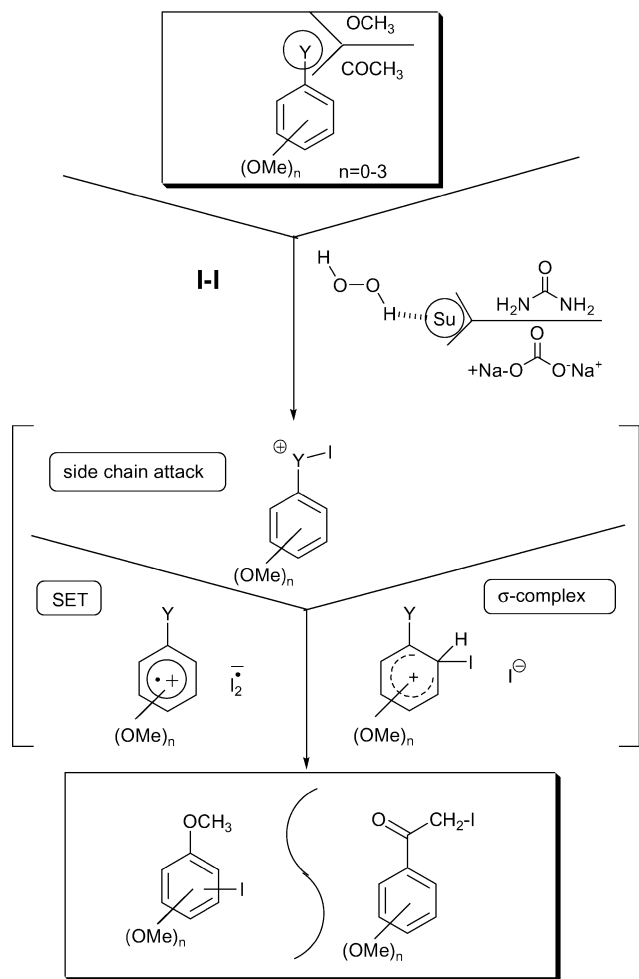
Scheme 1 Potentially reactive sites with possibly formed intermediates for electrophilic iodo-functionalisation of methoxy substituted benzene derivatives using I_2 in the presence of supported (Su) forms of H_2O_2.

Besides the convenience of a method for iodo-transformation performed under solvent-free conditions, the relation between the structure and aggregation state of the substrate and reaction conditions was carefully analysed. Additionally, the roles of two different H-bonded solid forms of H_2O_2 during the process of iodine introduction were investigated.

Results and discussion

The convenience of solvent-free iodination using elemental iodine and a supported form of H_2O_2 was first tested on mono-substituted aromatic compounds (Scheme 2). At this point we would like to stress that the term 'solvent-free' refers merely to the reaction itself. The workup process still involved the use of a solvent (t-BuOMe)

which, however, is considered a 'greener' substitute compared to widely-used harmful chlorinated solvents.

Aniline (**1a**) was chosen as a model substrate. In a blank experiment without the presence of any oxidiser and solvent, 4-iodo aniline (**2a**) was formed in 20% yield after 5 hours at room temperature (Table 1, entry 1); a slightly higher yield was obtained at 45 °C (entry 2). The presence of the urea–hydrogen peroxide (UHP) adduct remarkably affected the outcome of the reaction, promoting iodine introduction with high conversion and atom economy. In a typical experiment 0.5 mmol of finely powdered iodine was added to 1 mmol of substrate. The reaction mixture was vigorously shaken in order to obtain a good distribution between the reagent molecules, followed by the addition of 0.6 mmol of finely powdered UHP. An experiment performed at room temperature proceeded with 81% conversion to 4-iodo aniline (**2a**, entry 3), whereas maintaining the temperature at 45 °C for 5 hours resulted in a complete conversion to 4-iodo aniline (**2a**, entry 4). Sodium percarbonate (SPC) proved to be a less efficient mediator of iodination. After 5 hours of reaction between 1 mmol aniline, 0.5 mmol iodine and 0.6 mmol SPC, 65% conversion to 4-iodo aniline (**2a**) was found (entry 5); prolongation of the reaction time did not significantly improve the yield (entry 6).

To continue with the substrate of an aromatic ring activated toward electrophilic functionalisation, iodination of anisole (**1b**) under solvent-free conditions was examined. A reaction carried out for 7 hours at 45 °C using the ratio of substrate to iodine to UHP corresponding to 1 : 0.5 : 0.6 didn't provide any transformation of the substrate (entry 7). Prolonging the reaction time to 19 hours contributed to the introduction of iodine into anisole (**1b**) only moderately (entry 8). Also, increasing the amount of reagent just slightly improved the yield (entry 9).

Research was extended to monosubstituted aromatic compounds with a deactivated aromatic ring. The role of the UHP adduct in iodination of acetophenone (**1c**) was investigated. Besides the aromatic ring, the alkyl position in acetophenone is also a reactive site for electrophilic functionalisation, and thus the effect of reaction conditions on the regioselectivity of the transformation was of primary interest. Previously, it was reported that regioselective iodination of various acetophenones can be regulated by the solvent or generally by the polarity of the reaction system.[12] Our study showed that iodination of acetophenone can be accomplished under solvent-free conditions using the I_2–UHP combination. Iodine is regioselectively introduced into the alkyl position, indicating the polar character of the reaction system. In a blank experiment, no reaction occurred between acetophenone and iodine under solvent-free conditions after 6 hours at 45 °C (Table 1, entry 10), while electron-exchange took place in the presence of UHP, enabling the formation of 2-iodo-1-phenylethanone (**2c**). In order to elucidate the role of UHP, experiments were performed with various ratios of substrate to iodine to oxidiser (entries 10–19). Results showed that the highest conversion to **2c** was achieved using 1 mmol of iodine and 1 mmol UHP with 1 mmol of acetophenone after 6 hours (entry 17), consequently without atom economy of iodine introduction and indicating the role of UHP as an activator of the iodination process. In a reaction using SPC as the oxidiser, acetophenone remained unchanged after 7 hours at 45 °C (entry 19). During our investigations on the role of the reaction conditions and the atom economy concept of iodine introduction to various ketones,
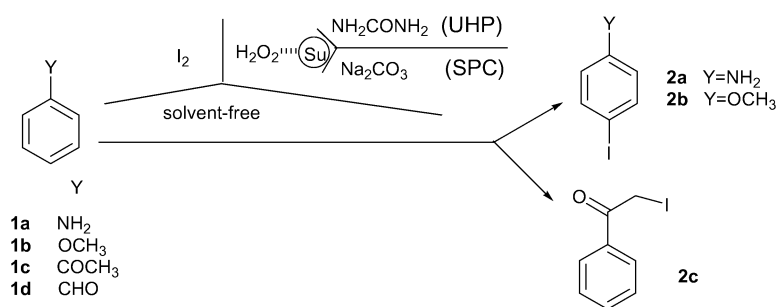
Scheme 2 Effect of functional groups and supported (Su) forms of H_2O_2 on the course of iodination with elemental iodine under solvent-free conditions.

Table 1

| Entry | Substrate | Oxiliser[a] | Reaction conditions | | | Yield[c] (%) |
			Molar ratio (substrate : I_2 : oxidiser)[b]	$T/°C$	t/h	
1	Y=NH$_2$ (**1a**)	—	1 : 0.5 : 0	25	5	50 (**2a**, 20)
2		—	1 : 0.5 : 0	45	5	50 (**2a**, 24)
3		UHP	1 : 0.5 : 0.6	25	5	81 (**2a**, 52)
4		UHP	1 : 0.5 : 0.6	45	5	100 (**2a**, 83)
5		SPC	1 : 0.5 : 0.6	45	5	65 (**2a**, 40)
6		SPC	1 : 0.5 : 0.6	45	18	74 (**2a**, 46)
7	Y=OCH$_3$ (**1b**)	UHP	1 : 0.5 : 0.6	45	7	0[d]
8		UHP	1 : 0.5 : 0.6	45	19	30 (**2b**, 8)
9		UHP	1 : 1 : 1	45	19	50 (**2b**, 16)
10	Y=COCH$_3$ (**1c**)	—	1 : 1 : 0	45	6	0[d]
11		UHP	1 : 0.3 : 0.3	45	6	36 (**2c**, 19, 22*)
12		UHP	1 : 0.5 : 0.6	45	3	55 (**2c**, 31, 42*)
13		UHP	1 : 0.6 : 0.6	45	6	62 (**2c**, 40)
14		UHP	1 : 0.6 : 0.6	45	17	69 (**2c**, 46)
15		UHP	1 : 1 : 0.3	45	6	56 (**2c**, 31, 39*)
16		UHP	1 : 1 : 0.6	45	6	71 (**2c**, 49)
17		UHP	1 : 1 : 1	45	6	89 (**2c**, 65)
18		UHP	1 : 1 : 1	45	3	72 (**2c**, 52, 53*)
19		SPC	1 : 0.5 : 0.6	45	7	0[d]
20	Y=CHO (**1d**)	UHP	1 : 1 : 1	45	20	0[d]

[a] UHP = urea–H_2O_2; SPC = $2Na_2CO_3–3H_2O_2$. [b] Molar ratio substrate : I_2 : H_2O_2. [c] The first number represents conversion determined from ^1H NMR spectra of crude reaction mixture, the first percentage in brackets represents isolated yield, the asterisked number is yield determined using 1,1-diphenylethene as internal standard. [d] Unreacted starting material.

we have already reported that iodination readily takes place under very moderate reaction conditions in aqueous medium using I_2–30% aq. H_2O_2.[11b] However, this paper was overlooked in a recently published unusual procedure based on an enormous iodine excess (susbstrate : I_2 amounting to 1 : 4) performed in dimethoxyethane (bp 85 °C) heated at 90 °C for 3 hours.[13]

Benzaldehyde (**1d**) was chosen as another molecule bearing a deactivated aromatic ring in addition to the fact that the aldehyde functionality is prone to oxidation. Nevertheless, after 20 hours at 45 °C using I_2–UHP in a solventless system, only the starting substrate was isolated from the reaction mixture (entry 20). From those initial experiments, it is evident that the structure of the various forms of H_2O_2 plays a significant role in the introduction of iodine into organic molecules. Urea–H_2O_2 (UHP) was found to be substantially more effective than sodium percarbonate (SPC) in all cases of iodination under solvent-free conditions.

Furthermore, we studied the effect of reaction conditions on the iodination of 4-t-Bu-phenol (**3**, Table 2). A substrate in a solid ag-

gregate state at room temperature is known to potentially undergo electrophilic substitution at the *ortho* position to the phenolic group, *ipso*-substitution at position 4 and addition processes.[14] Moreover, due to its high reactivity a tendency toward formation of the diiodo product was expected. In a blank experiment, in which no oxidiser was present, no reaction between the substrate (**3**) and iodine under solvent-free conditions at 45 °C after 5 hours took place (Table 2, entry 1), while progressive electron exchange occurred in the presence of UHP as oxidiser at 45 °C. After 5 hours at 45 °C with a ratio of substrate to iodine to UHP corresponding to 1 : 0.5 : 0.6 under neat conditions, 50% of 2-iodo-4-t-Bu-phenol (**4a**), 25% of 2,6-diiodo-4-t-Bu-phenol (**4b**) and 25% of unreacted substrate were present in the reaction mixture (entry 4). Raising the amount of reagent resulted in a complete conversion of 4-t-Bu-phenol (**3**), but regulation of selectivity to either the monoiodinated or diiodinated product was not achieved (entry 5). Even with a significant excess of reagent (1.3 mmol I_2, 1.3 mmol UHP) at 45 °C after 6 hours, 17% of monoiodinated product

Table 2 Effect of reaction conditions on mono- and di-iodination of 4-*t*-Bu-phenol (**3**) without the use of a solvent

		Reaction conditions				
Entry	Oxidiser[a]	Molar ratio (substrate : I$_2$: oxidiser)[b]	$T/°C$	t/h	Conversion (%)[c]	Ratio **4a** : **4b**
1	—	1 : 1 : 0	45	5	0	—
2	UHP	1 : 0.5 : 0.6	25	5	10	1 : 0
3	UHP	1 : 1 : 1	25	6	25	1 : 0
4	UHP	1 : 0.5 : 0.6	45	5	75	2 : 1
5	UHP	1 : 1 : 1	45	6	100	1 : 2.3
6	UHP	1 : 1.3 : 1.3	45	6	100	1 : 4.9
7	SPC	1 : 0.5 : 0.6	45	6	14	1 : 1
8	SPC	1 : 1 : 1	45	6	23	1 : 1.1
9	SPC	1 : 1.3 : 1.3	45	6	35	1 : 1.5

[a] UHP = urea–H$_2$O$_2$; SPC = 2Na$_2$CO$_3$–3H$_2$O$_2$. [b] Molar ratio substrate: I$_2$: H$_2$O$_2$. [c] Conversion determined from ^{1}H NMR spectra of crude reaction mixture.
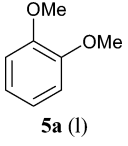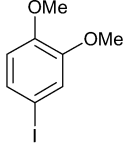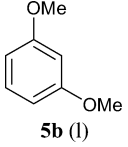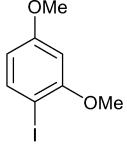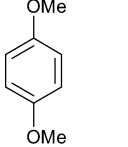
was still present in addition to 83% of diiodinated product in the reaction mixture (entry 6). An attempt to obtain only the monoiodinated product with an excess of reagent by lowering the temperature to room temperature also failed, since only moderate conversion to 2-iodo-4-*t*-Bu-phenol (**4a**) was achieved (entries 2, 3). Despite the poorly controllable regioselectivity, the atom economy aspect of the transformation should be stressed. Both iodine atoms of the elemental iodine molecule were consumed in the presence of UHP as an oxidiser. UHP was found to be superior to SPC as an oxidiser under solvent-free conditions in this case as well, since conversions and selectivities of iodo-transformations using SPC as a mediator of iodination were considerably lower than in the case of UHP (entries 7–9).

In our previous study we demonstrated the effect of different solvents and two oxidisers, namely F-TEDA-BF$_4$ and a 30% aqueous solution of H$_2$O$_2$, on the iodo-functionalisation of dimethoxy benzenes.[11h] The differences in reactivity of the methoxy-substituted compounds could be illustrated by the values of the halfway potential,[15] indicating the possibility of the formation of their cation-radicals, the stability of which is known to importantly direct further transformation.[16] In the same above-mentioned study, two distinct reaction routes, requiring different ratios of substrate to iodine to oxidiser and leading to iodo-products, were proposed. Dimethoxy benzenes (Table 3) and trimethoxy benzenes (Table 4) were also chosen as model substrates for the present study in order to obtain insight into the reaction pathway of iodination under solvent-free conditions using solid carriers of H$_2$O$_2$ as mediators of iodination. In blank experiments, where no oxidiser was present, conversions of substrates were either very low or formation of a polymeric material was noticed. On the other hand, the presence of UHP contributed considerably to the efficiency and high atom-economy of iodo-transformation in all cases, except in the case of 1,4-dimethoxy benzene (**5c**), where even after a longer reaction time at 45 °C the starting material remained unchanged (Table 3, entry

9). Our results showed that a molar ratio of substrate to iodine to UHP of 1 : 0.5 : 0.6 was sufficient for the introduction of iodine into 1,2-dimethoxy benzene (**5a**) and 1,3-dimethoxy benzene (**5b**) with relatively high conversion after 7 hours at 45 °C without the use of any solvent (entries 2, 6), while 1,4-dimethoxy benzene (**5c**) remained unchanged even after 23 hours at 45 °C with a ratio of substrate to iodine to UHP of 1 : 1 : 1 under solvent-free conditions (entry 9). In the case of 1,2-dimethoxy benzene (**5a**), the yield was further improved by employment of an equimolar amount of I$_2$ and UHP with respect to the substrate (entry 3).
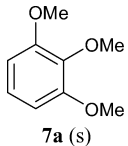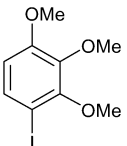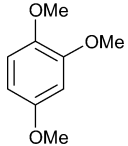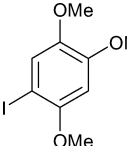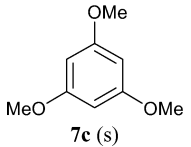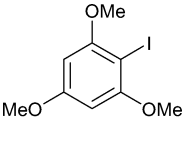
High conversions to iodo-products were achieved in all cases of trimethoxy benzenes (**7a**, **7b**, **7c**) by the use of only a 0.5 molar equivalent of I$_2$ and 0.6 molar equivalents of UHP at 45 °C without the use of solvent (Table 4, entries 2, 3, 7, 8, 11), thus providing reactions of high atom economy in regard to iodine and indicating an ionic route of transformation through the formation of a δ-complex. It is evident that UHP plays a dual role in such cases, acting as an activator in the first step and as an oxidant of iodide to iodine in the next step. The results on the route of iodo-transformation with regard to the structure of dimethoxy- and trimethoxy benzenes are in accordance with conclusions on iodination using water as reaction medium and 30% aqueous solution of H$_2$O$_2$ as an oxidiser for **5a**, **5b**, **6a**, **6b**, **6c**.[11h,11i] A noticeable difference should be pointed out for **5c**, namely the possibility of ion-radical formation in water, while under solventless conditions iodo-functionalisation through the formation of ion-radicals does not seem feasible. This observation lead us to conclude that the reaction system I$_2$–UHP–no solvent is not convenient for the formation of ion-radicals, while an alternative explanation could be connected with the solid aggregate state of 1,4-dimethoxy benzene (**5c**), which might circumvent transformation in this particular case. However, it is interesting to note that substrate **5c** with the lowest one-electron oxidation potential ($E_{1/2} = 1.30$ V)[15] was not transformed, while **5a** and **5b**, requiring higher energy ($E_{1/2}$ for **5a** and **5b** were

Table 3 Effect of the structure of dimethoxy benzenes, their aggregate state and reaction conditions on iodination under solvent-free conditions

Entry	Substrate[a]	Oxidiser[b]	Reaction conditions Molar ratio (substrate : I₂ : oxidiser)[c]	$T/°C$	t/h	Product	Yield (%)[d]
1		—	1 : 1 : 0	45	7		27 (9)
2		UHP	1 : 0.5 : 0.6	45	7		63 (40)
3		UHP	1 : 1 : 1	45	7		91 (75)
4	5a (l)	SPC	1 : 1 : 1 1 : 1 : 1	45	7	6a	0[e]
5		—	1 : 1 : 0	45	7		15 (7)
6		UHP	1 : 0.5 : 0.6	45	7		78 (67)
7		SPC	1 : 0.5 : 0.6	45	7		39 (21)
8	5b (l)	SPC	1 : 1 : 1	45	7	6b	65 (39)
9		UHP	1 : 1 : 1	45	23		0[e]
10	5c (s)	SPC	1 : 1 : 1	45	23		0[e]

[a] Aggregate state at room temperature in parentheses, (l) liquid; (s) solid. [b] UHP = urea–H₂O₂; SPC = 2Na₂CO₃–3H₂O₂. [c] Molar ratio substrate : I₂ : H₂O₂. [d] The first number represents conversion determined from ¹H NMR spectra of crude reaction mixture, the bracketed number represents isolated yield. [e] Unreacted starting material.

Table 4 Effect of the structure of trimethoxy benzenes, their aggregate state and reaction conditions on iodination without the use of a solvent

Entry	Substrate[a]	Oxidiser[b]	Reaction conditions Molar ratio (substrate : I₂: oxidiser)[c]	$T/°C$	t/h	Product	Yield (%)[d]
1		—	1 : 1 : 0	45	5		PM[e]
2		UHP	1 : 0.5 : 0.6	45	5		76 (61)
3		UHP	1 : 0.5 : 0.6	45	18		90 (58)
4		UHP	1 : 1 : 1	45	5		100 (82)
5	7a (s)	SPC	1 : 1 : 1	45	6	8a	0[f]
6		—	1 : 1 : 0	45	5		PM[e]
7		UHP	1 : 0.5 : 0.6	45	5		70 (50)
8		UHP	1 : 0.5 : 0.6	45	17		81 (58)
9	7b (l)	SPC	1 : 1 : 1	45	6	8b	41 (15)
10		—	1 : 1 : 0	45	5		25 (12)
11		UHP	1 : 0.5 : 0.6	45	55		100 (89)
12	7c (s)	SPC	1 : 0.5 : 0.6	45	5	8c	71 (52)

[a] Aggregate state at room temperature in parentheses, (l) liquid; (s) solid. [b] Oxidiser: A = urea–H₂O₂; B = 2Na₂CO₃–3H₂O₂. [c] Molar ratio substrate : I₂ : H₂O₂. [d] The first number represents conversion determined from ¹H NMR spectra of crude reaction mixture, the bracketed number represents isolated yield. [e] Polymeric material. [f] Unreacted starting material.

established to be 1.44 V and 1.58 V, respectively)[15] were successfully iodinated. SPC again proved to be less convenient as a mediator of iodination without the use of a solvent, since considerably lower conversions to iodinated products were achieved (Table 3, entries 8, 10 and Table 4, entries 9, 12). Moreover, in the cases of 1,2-dimethoxy benzene (**5a**) and 1,2,3-trimethoxy benzene (**7a**) no reaction occurred (Table 3, entry 4 and Table 4, entry 5).

Methoxy substituted acetophenones offer a further possibility for studying the regioselectivity of the transformation. The methoxy substituted acetophenones investigated in the current research (**9a–d**, Table 5) were regioselectively iodinated at the alkyl position of the acetophenone-moiety using the I_2–UHP combination under solvent-free conditions, except for 1-(2,4-dimethoxyphenyl)ethanone, where a mixture of 1-(2,4-dimeth-oxyphenyl)-2-iodoethanone, 1-(3-iodo-4,5-dimethoxyphenyl)-ethanone and 2-iodo-1-(3-iodo-4,5-dimethoxyphenyl)ethanone was formed. To clarify the role of UHP, reactions were performed with different amounts of I_2 and UHP in regard to substrates **9a**, **9b**, **9c**, **9d** and also the effect of reaction time on the efficiency of the transformation was verified (Table 5). Blank experiments, where only the substrate and iodine were heated at 45 °C for 6 hours without the presence of a solvent and UHP, showed either low conversion (entry 9) or no conversion at all (entries 1, 17, 25). The results demonstrated that the presence of UHP facilitated the introduction of iodine at the alkyl position of methoxy substituted acetophenones. The highest conversion to iodinated products for **9a**, **9c** and **9d** was achieved with a molar ratio of substrate to iodine to UHP of 1 : 1 : 1 (entries 8, 22,

Table 5 Effect of the structure of methoxy-substituted acetophenones and reaction conditions on side-chain iodination under solvent-free conditions


Entry	Substrate	Reaction conditions		Yield (%)[b]
		Molar ratio substrate : I_2 : oxidiser[a]	T/h	
1	COCH₃ (9a)	1 : 1 : 0	6	0[c]
2		1 : 0.3 : 0.3	6	26 (15, 23*)
3		1 : 0.5 : 0.6	3	52 (35, 44*)
4		1 : 0.5 : 0.6	6	48 (28, 31*)
5		1 : 1 : 0.3	6	33 (16, 21*)
6		1 : 1 : 0.6	6	56 (32. 38*)
7		1 : 1 : 1	3	73 (54, 61*)
8		1 : 1 : 1	6	79 (54, 58*)
9	COCH₃ (9b)	1 : 1 : 0	6	17 (7)
10		1 : 0.3 : 0.3	6	50 (28, 31*)
11		1 : 0.5 : 0.6	3	50 (23, 30*)
12		1 : 0.5 : 0.6	6	46 (25, 30*)
13		1 : 1 : 1	3	37 (16, 21*)
14		1 : 1 : 1	6	37 (18, 23*)
15		1 : 1 : 0.6	6	47 (28, 34*)
16		1 : 1 : 0.3	6	44 (26, 33*)
17	COCH₃ (9c)	1 : 1 : 0	6	0[c]
18		1 : 0.3 : 0.3	6	36 (21, 20*)
19		1 : 0.5 : 0.6	3	53 (35, 36*)
20		1 : 0.5 : 0.6	6	78 (55, 59*)
21		1 : 1 : 1	3	77 (51, 55*)
22		1 : 1 : 1	6	88 (58, 60*)
23		1 : 1 : 0.6	6	60 (37, 42*)
24		1 : 1 : 0.3	6	39 (24, 25*)
25	COCH₃ (9d)	1 : 0.5 : 0.6	6	0[c]
26		1 : 1 : 1	6	17 (9)
27		1 : 1 : 1	17	34 (22)

[a] Molar ratio substrate : I_2 : H_2O_2. [b] The first number represents conversion determined from ^{1}H NMR spectra of crude reaction mixture, the first bracketed number represents isolated yield; the asterisked number is yield determined using 1,1-diphenylethene as internal standard. [c] Unreacted starting material.

27), which highlights UHP in the role of an activator of the iodinating system under solvent-free conditions for these methoxy substituted acetophenones. The atom economy principle was not followed in these cases. In this respect, results of iodination under solvent-free conditions using the I_2–UHP reagent system differ from observations of iodine introduction using I_2, a 30% aqueous solution of H_2O_2 as an oxidiser and water as reaction medium.[11i] In the latter case, high conversions to side-chain iodinated products were obtained with 0.5 molar equivalent of reagent. An exception to the behaviour of **9a** and **9c** was observed in the case of 1-(3,4-dimethoxyphenyl)ethanone (**9b**), where introduction of iodine under solventless conditions was more efficient when the ratio of substrate to iodine to UHP was 1 : 0.5 : 0.6 compared to the 1 : 1 : 1 ratio, but the conversion was still only moderate (entries 11, 12).

In order to study the effect of ketone structure, the investigation was additionally extended to cyclic alkyl aromatic ketones. The introduction of iodine under solvent-free conditions proved to be very efficient in the case of 1-indanone (**11a**) and 1-tetralone (**11b**) as depicted in Scheme 3. Reacting 1 mmol of 1-indanone (**11a**) with 0.5 mmol of iodine and 0.6 mmol of UHP with no use of solvent for 5 hours at room temperature resulted in 55% formation of 2-iodo-1-indanone (**12a**), while 2-iodo-1-tetralone (**12b**) was formed with 0.5 mmol of I_2 and 0.6 mmol of UHP after 6 hours at room temperature with 40% conversion. Raising the temperature to 45 °C with the same ratio of substrate to iodine to UHP and the same reaction time remarkably improved the conversion in both substrates. Thus, 1-indanone (**11a**) was 80% converted to 2-iodo-1-indanone (**12a**) and 2-iodo-1-tetralone (**12b**) was formed from 1-tetralone (**11b**) with 90% conversion.
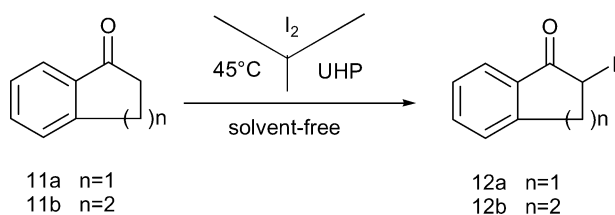
Scheme 3 Introduction of iodine into the α-alkyl position of 1-indanone and 1-tetralone with molecular iodine in the presence of UHP under solvent-free conditions.

A further extension of the investigation focused on methoxy substituted benzaldehydes (3,4-dimethoxybenzaldehyde, 2,3,4-trimethoxybenzaldehyde and 3,4,5-trimethoxybenzaldehyde), but no or a very low amount of iodinated product was found in the case of 3,4-dimethoxy-benzaldehyde even after 18 hours at 45 °C with the ratio of substrate : iodine : UHP of 1 : 1 : 1.

Finally, we discovered that addition of iodine to some alkenes and phenyl acetylenic derivatives efficiently proceeds under solvent-free conditions without the need for an oxidiser at room temperature (Scheme 4). This significantly contributes to a 'green' addition protocol since the reaction is completely atom economic and no additional reagent, solvent or energy requirements are needed. 1-octene (**13a**) was 93% converted to 1,2-diiodo-octane (**14a**) with 1 molar equivalent of iodine after 5 hours at room temperature under solvent-free conditions, yielding 65% of product after isolation. The addition of iodine to phenyl-acetylenes under solventless conditions was found to be *trans*-oriented.
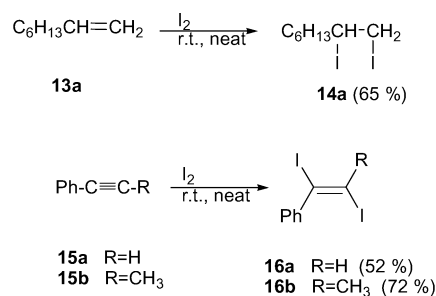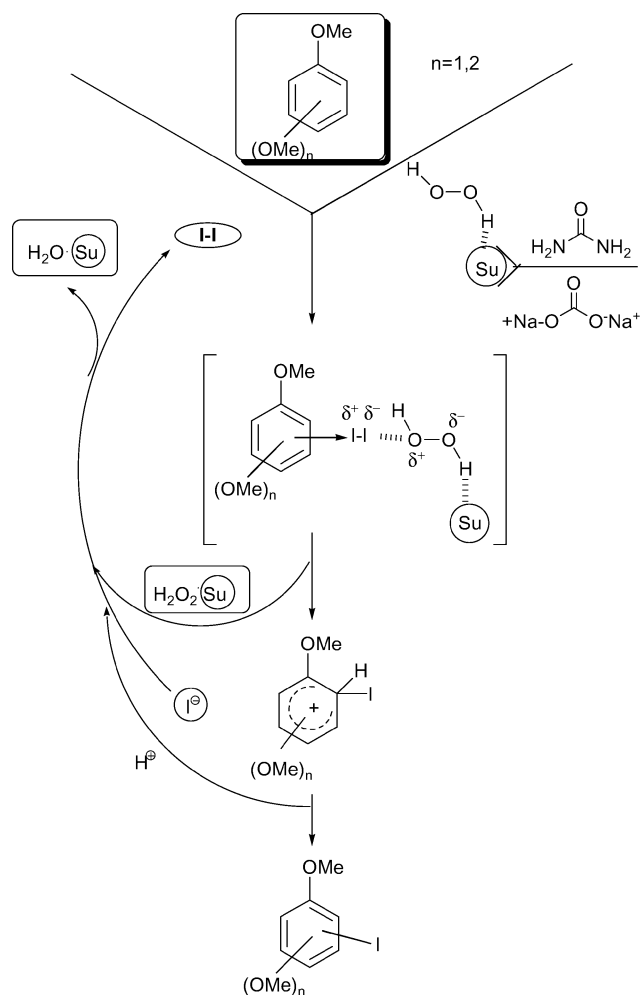

Scheme 4 Effect of reaction conditions on addition of iodine to alkenes and phenyl acetylenes under solvent-free conditions.

As determined from ^1H NMR spectra of the crude reaction mixture, phenyl acetylene (**15a**) was converted to *trans*-(1,2-diiodovinyl)benzene (**16a**) and 1-phenyl-1-propyne (**15b**) to *trans*-(1,2-diiodopropenyl)benzene (**16b**) with 94 and 98% conversion, respectively, after 6 hours at room temperature without the use of any oxidiser or solvent, yielding 52 and 72% of isolated products.

Conclusions

The introduction of iodine using elemental iodine in the presence of the urea–hydrogen peroxide adduct (UHP) under solvent-free conditions and without the need for any metal or acid catalyst proved to be feasible for several organic compounds activated toward electrophilic functionalisation, namely aniline (**1a**), p-*t*-Bu-phenol (**3**), dimethoxy- and trimethoxy benzenes (**5a**, **5b**, **7a**, **7b**, **7c**), acetophenones (**1b**, **9a**, **9b**, **9c**), 1-indanone (**11a**) and 1-tetralone (**11b**). Sodium percarbonate (SPC) as a mediator of iodination showed inferiority compared to UHP, since significantly lower conversions to iodinated products were obtained. The site of iodo-functionalisation was found to be crucially dependant on the structure of the substrate, while its efficiency could be further regulated by the amount of reagent, reaction time and temperature. Based on the required ratio of substrate to iodine to oxidiser for the most efficient iodo-transformation, two reaction routes were established and the roles of UHP elucidated in each route. The one requiring a 1 : 0.5 : 0.6 molar ratio for achieving the highest efficiency of iodine introduction follows atom economy in regard to iodine and proceeds through an ionic mechanism with σ-complex formation in the intermediate stage (Scheme 5). The iodide ion liberated after initial electrophilic attack of iodine is oxidised by UHP in the second stage, thus providing regenerated iodine for a second electrophilic attack on the substrate. The dual role of UHP as an activator of the iodinating system and regenerator of iodine is evident in these cases, which were present in iodination of aniline (**1a**), p-*t*-Bu-phenol (**3**), 1,2-dimethoxy benzene (**5a**), 1,3-dimethoxy benzene (**5b**), 1,2,3-trimethoxy benzene (**7a**), 1,2,4-trimethoxy benzene (**7b**), 1,3,5-trimethoxy benzene (**7c**), 1-indanone (**11a**) and 1-tetralone (**11b**).

On the other hand, atom economy was not attained in the cases of acetophenone (**1c**) and methoxy-substituted acetophenones (**9a**, **9b**, **9c**, **9d**), where the highest conversion to side-chain iodinated product was achieved with a ratio of substrate to iodine to UHP corresponding to 1 : 1 : 1. In these cases, UHP is believed to play only the role of an activator of the iodinating system (Scheme 6). Moreover, addition of iodine to 1-octene (**13a**),

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Scheme 5 Suggested reaction route for efficient iodination of dimethoxy- and trimethoxy benzenes with the required ratio of substrate to I_2 to UHP corresponding to 1 : 0.5 : 0.6 under solvent-free conditions.

phenylacetylene (**15a**) and 1-phenyl-1-propyne (**15b**) was found to proceed efficiently without the need of any oxidiser and solvent at room temperature.

Finally, we would like to stress the 'green' approach of the method in addition to its simplicity and mildness. Avoidance of solvent for performing reactions, the use of a non-toxic, relatively cheap, safe and stable oxidiser, its benign by-product of oxidation and atom economy achieved in most cases are valuable attributes. Since the listed attributes are also desirable characteristics in a wider scientific context and in industrial chemical processes, we believe that the results of this research might find application on a more extensive scale, with considerably lower financial and environmental impact than using other previously reported iodination methods.

Experimental

Iodine, UHP, SPC and substrates were purchased from Sigma Aldrich. Solid reagents and substrates were finely powdered in a mortar before use, while liquid substrates were used as received. *t*-BuOMe was purchased from Riedel-de-Haën, other chemicals (Na_2SO_4 and $Na_2S_2O_3$) from Merck and were used as received. [1]H
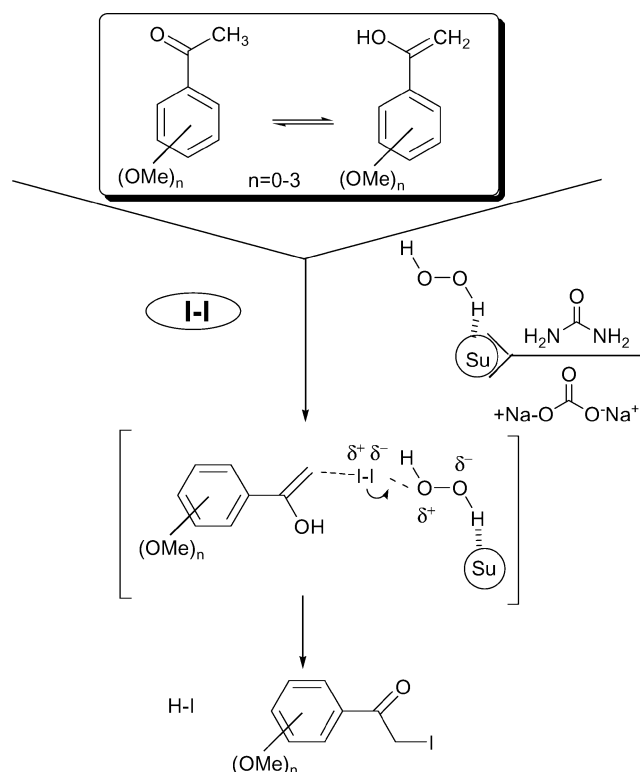
Scheme 6 Suggested reaction route for iodination of methoxy-substituted acetophenones with required ratio of substrate to I_2 to UHP corresponding to 1 : 1 : 1 under solvent-free conditions.

NMR spectra were recorded on a Varian INOVA 300 spectrometer at 300 MHz. 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 AutospecQ instrument under EI conditions at 70 eV.

General procedure

Finely powdered iodine (127 mg, 0.5 mmol; 254 mg, 1 mmol; 76 mg, 0.3 mmol; 330 mg, 1.3 mmol, see Tables 1–5) was added to the neat liquid substrate (1 mmol) or finely powdered substrate in cases of solid compounds. After shaking the mixture vigorously to obtain a good distribution between substrate and iodine molecules in a 5-mL round-bottom flask, finely powdered oxidiser UHP (56.4 mg, 0.6 mmol; 94 mg, 1 mmol; 28.2 mg, 0.3 mmol; 125 mg, 1.3 mmol, see Tables 1–5) or SPC (63 mg, 0.4 mmol; 110 mg, 0.7 mmol; 141 mg, 0.9 mmol containing 20.4 mg, 0.6 mmol; 34 mg, 1 mmol; 44 mg, 1.3 mmol of active oxidant H_2O_2, respectively, see Tables 1–4) was added. The reaction mixture was again vigorously shaken to enable a good contact between reacting molecules. Pulverization of solid compounds was made in a mortar prior to their transfer to the 5-mL round-bottom flask. Reactions were carried out either at room temperature or at 45 °C for various times (3–23 h, see Tables 1–5), followed by extraction of products with *t*-BuOMe (20 mL). The organic phase was washed with an aqueous solution of $Na_2S_2O_3$ (10%, 20 mL) to destroy unreacted iodine, H_2O (20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixtures were analysed by TLC, ^{1}H NMR and mass spectroscopy and products identified on

the basis of comparison with their spectroscopic data with the literature.[4f,11a,17,18] Conversions and yields of iodinated products obtained are listed in Tables 1–5.

Iodination of 1,3,5-trimethoxy benzene (7c). No solvent was used during performance of the reaction and product isolation in the case of iodination of 1,3,5-trimethoxy benzene (**7c**) using UHP as mediator of oxidation. Prior to the reaction performance, substrate **7c**, iodine and UHP were separately finely triturated in a mortar, after which each was transferred to a 5-mL round-bottom flask, where the reaction was performed. To the finely powdered substrate **7c** (168 mg, 1 mmol), finely powdered iodine (127 mg, 0.5 mmol) was first added. Vigorous shaking was followed by the addition of UHP (56.4 mg, 0.6 mmol), and more strong shaking of the reaction mixture ensued. After 5 hours reaction at 45 °C, an aqueous solution of $Na_2S_2O_3$ (10%, 30 mL) was poured into the reaction mixture and the solution obtained was vigorously stirred for an hour at room temperature. Following filtration under reduced pressure, only 2-iodo-1,3,5-trimethoxy benzene (**8c**, 263 mg, 0.89 mmol) was present in the isolated mixture.

Addition of iodine to 1-octene (13a), phenylacetylene (15a) and 1-phenyl-1-propyne (15b). Iodine was finely powdered in a mortar, after which 254 mg (1 mmol) was transferred to a 5-mL round-bottom flask containing the liquid substrate (1 mmol). The mixture was strongly shaken and left to react at room temperature. After 5–6 hours products were extracted with *t*-BuOMe (20 mL). The organic phase was washed with an aqueous solution of $Na_2S_2O_3$ (10%, 20 mL), H_2O (20 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixtures were analysed by TLC, ^{1}H NMR and mass spectroscopy and products identified on the basis of comparison of their spectroscopic data with the literature.[19,20] Yields of the iodinated products obtained are depicted in Scheme 4.

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