

Scientific paper

Iodination of Organic Compounds Using the Reagent System I_2 –30% aq. H_2O_2 under Organic Solvent-free Reaction Conditions

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Dedicated to the memory of Professor Ljubo Golič

Abstract

Iodine was efficiently introduced into the methoxy substituted aromatic compounds, acetophenone, 1-indanone and 1-tetralone using the elemental iodine / 30% aq. H_2O_2 system under organic solvent-free reaction conditions (SFRC) and two types of iodo-functionalisation through an electrophilic process were observed. Iodination of the aromatic ring in the case of dimethoxy- and trimethoxy benzenes took place, while aryl alkyl ketones were regioselectively iodinated at the alkyl position next to a carbonyl group. Based on the ratio of substrate : I_2 : H_2O_2 required for the most efficient iodo-transformation, two different roles of H_2O_2 in the reaction route can be distinguished. Different forms of H_2O_2 as mediators of iodination, namely 30% aq. H_2O_2 and two solid forms urea- H_2O_2 and sodium percarbonate ($2Na_2CO_3 \cdot 3H_2O_2$), were comparatively evaluated in terms of efficiency under SFRC. Reactions using 30% aq. H_2O_2 as the mediator of iodination under SFRC were compared with those performed in water as reaction medium.

Keywords: Green chemistry, halogenation, iodination, hydrogen peroxide, solvent-free

1. Introduction

Compared to the other halogens, iodine is the most bulky, the least electronegative, the most polarizable and forms the weakest carbon-halogen bond.¹ As a consequence of these properties, iodo-substituted organic compounds have found important application as synthons or precursors in organic synthesis, mainly for C–C and C–N bond formation, which has been used for the synthesis of several natural products and bioactive compounds.² Moreover, iodinated compounds can be used as radioactively labelled markers or contrastors in medical diagnosis.³

Elemental iodine is scarcely reactive enough for efficient introduction into organic molecules in an electrophilic manner. However, the presence of an appropriate oxidant can significantly enhance its reactivity and thus aid in the efficiency of the transformation. Numerous methods employing iodonium donating agents have been de-

veloped over the years⁴ and have been recently reviewed.⁵ Many of them employ harsh reaction conditions, such as ample use of strong acids in combination with an iodinating agent, or the use of heavy metal salts or oxides as activators of iodine. These methods require special safety precautions during experimental handling and represent serious concerns regarding environmental and health issues. The last decade has prompted the wider community to a deeper awareness of sustainable development, which in science lead to the movement known under the term 'green' chemistry.⁶ According to the 12 principles of green chemistry, prevention and avoidance of hazard, rather than treatment, should be of utmost importance. Contrary to traditional perception of the necessity of an appropriate organic solvent for performing reaction, in terms of a green chemistry approach, the best solvent is regarded as 'no solvent at all'.⁷ Thus, solvent-free reactions have gained increased attention in recent years.⁸ Their advanta-

ges over conventional methods in many cases include enhanced efficiency and selectivity, cleaner products, milder reaction conditions, reduction of reaction times and simplified procedures. There have not been many reports on iodination without the presence of an organic solvent.⁹ In our current study, a 30% aqueous solution of hydrogen peroxide was used as an oxidant and mediator of iodination. Due to the formation of water as a benign by-product of oxidation, hydrogen peroxide is considered to be a 'green' oxidant.¹⁰ Other advantageous properties such as wide availability, relative inexpensiveness, ease of handling, and stability at room temperature makes it a desirable oxidant, which moreover resulted in its comprehensive application in several oxidation systems.¹¹ In our on-going efforts to develop environmentally friendlier halogenation procedures,¹² we now report a further investigation dealing with the iodination of organic compounds using the reagent system I_2 / 30% aq. H_2O_2 without the presence of an organic solvent for performing reactions.

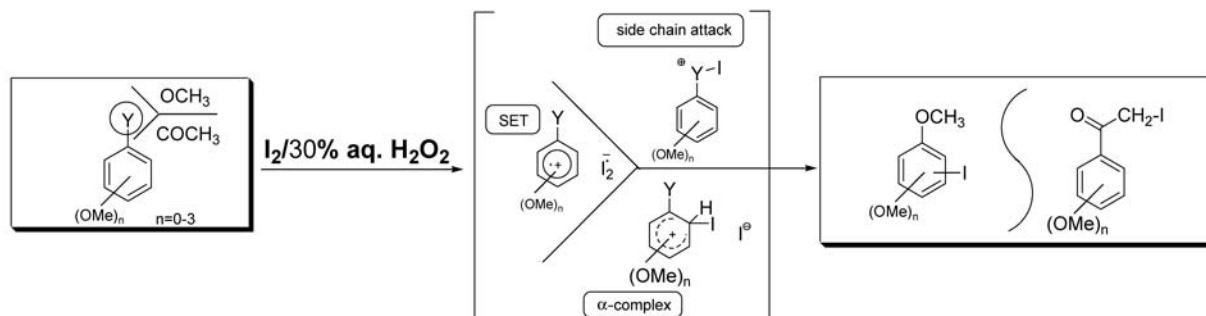
2. Results and Discussion

As regards the scope of the substrates, methoxy-substituted aromatic derivatives were chosen as feasible substrates for investigating the course of transformation because of the known fact that an activated aromatic ring of some of the chosen substrates is prone to ion-radical formation with various oxidising agents.¹³ Furthermore, the acetophenone moiety was selected for studying the regioselectivity of the transformation. Based on the selection of substrates, iodo-transformation was anticipated to proceed through 3 different intermediates, while iodo-functionalisation was expected to take place either on the aromatic ring or on the side-chain in the case of aryl alkyl ketones (Scheme 1). As in our previous experience, an ionic mechanism with the formation of a σ -complex in the intermediate stage was assumed to be differentiated from a SET process with ion-radical formation on the basis of the amount of reagent used.^{9e, 12f}

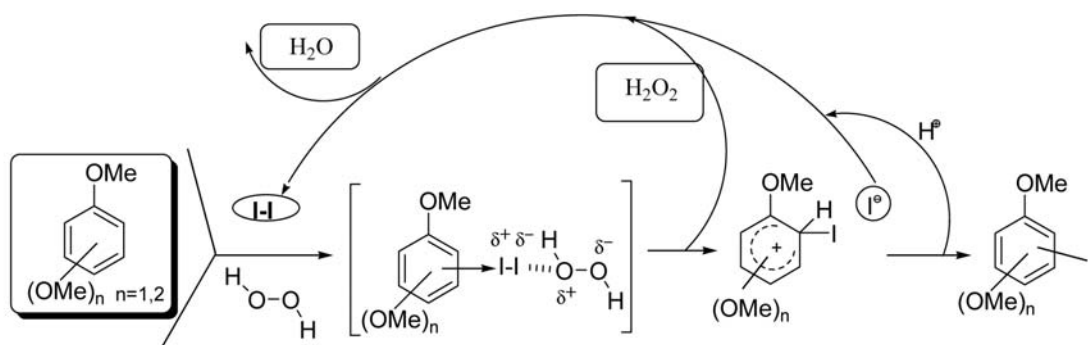
The adequacy of the method for iodination with 30% aq. H_2O_2 as a mediator and without the presence of an organic solvent was initially tested on the most reactive substrate toward electrophilic attack among the trimet-

hoxy substituted benzenes, namely 1,3,5-trimethoxy benzene (**6**). A blank experiment without the presence of any oxidiser performed with 0.5 molar equivalent of molecular iodine at 45 °C for 5 hours showed no conversion to iodinated products, while 25% conversion to 2-iodo-1,3,5-trimethoxy benzene (**6a**) was established when 1 molar equivalent of iodine was used. In the presence of 30% aq. H_2O_2 the result of the reaction was significantly different. 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 active H_2O_2 as a 30% aq. solution. After 5h heating at 45 °C crude 2-iodo-1,3,5-trimethoxy benzene (**6a**) was quantitatively obtained, thus providing to high atom economy in respect to iodine (entry 10, Table 1) under such solvent-free reaction conditions (SFRC). Encouraged by this result, the method was further evaluated for other trimethoxy- and dimethoxybenzenes (**1–5**, Table 1). The differences in reactivity of the chosen substrates can be illustrated by the values of their half-way potential,¹⁴ indicating the possibility of the formation of ion-radicals, which can crucially affect further transformation. In our previous studies, two distinct routes explaining the role of an oxidiser in combination with elemental iodine in iodination process were suggested.^{9e, 12f} They can be experimentally differentiated by the amount of reagent used for efficient transformation. In all cases of trimethoxy benzenes the ratio of substrate : I_2 : oxidant corresponding to 1 : 0.5 : 0.6 was sufficient for high conversion to iodinated products at 45 °C for 5h under SFRC (entries 7, 9, 10, Table 1). As both iodine atoms of the molecule are consumed in these cases, it contributes to the high atom economy in regard to iodine, which is a valuable attribute from the 'green' chemistry aspect. These reactions are believed to proceed through an ionic mechanism with the formation of a σ -complex in the intermediate stage. The role of hydrogen peroxide is dual in these cases, acting as an activator in the first step and as an oxidant of liberated iodide to iodine in the next step (Scheme 2).

The behaviour of 1,3-dimethoxy benzene (**2**) was similar to trimethoxy benzenes being 92% converted to 4-iodo-1,3-dimethoxy benzene (**2a**) with 0.5 molar equivalent of the reagent system I_2 /30%aq. H_2O_2 after 5 hours at



Scheme 1



Scheme 2

Table 1 Iodination of di- and trimethoxy substituted benzene derivatives using the $I_2/30\%$ aqueous H_2O_2 system under SFRC.

| Entry | Substrate | Ratio ^a | Time (h) | Product | Conv. ^b (%) | Yield (%) ^c |
|-------|-----------|--------------------|----------|-----------|------------------------|------------------------|
| | | | | | | |
| 1 | | 1 : 0.5 : 0.6 | 7 | | 65 | 44 |
| 2 | 1 | 1 : 1 : 0 | 7 | 1a | 82 | 60 |
| 3 | | 1 : 0.5 : 0.6 | 5 | | 92 | 78 |
| 4 | | 1 : 0.5 : 0.6 | 7 | | 0 | 0 |
| 5 | | 1 : 1 : 1 | 7 | | 0 | 0 |
| 6 | 3 | 1 : 1 : 1 | 23 | 3a | 0 | 0 |
| 7 | | 1 : 0.5 : 0.6 | 5 | | 87 | 69 |
| 8 | 4 | 1 : 1 : 1 | 5 | 4a | 100 | 79 |
| 9 | | 1 : 0.5 : 0.6 | 5 | | 92 | 52 |
| 10 | | 1 : 0.5 : 0.6 | 5 | | 100 | 70 |
| | 6 | | | 6a | | |

^a Molar ratio substrate : I_2 : H_2O_2 . ^b Conversion determined from the 1H NMR spectra of crude reaction mixtures. ^c Yield of isolated pure product.

45 °C without the presence of an organic solvent (entry 3, Table 1). On the other hand, a whole molar equivalent

amount of I₂ was necessary for more efficient iodofunctionalisation of 1,2-dimethoxy benzene **1** (Entry 1, Table 1),

Table 2: Iodination of aryl alkyl ketones using the I₂ / 30% aqueous H₂O₂ system under SFRC

| Entry | Substrate | Ratio ^a | Time (h) | Yield (%) ^b |
|-------|-----------|--------------------|----------|------------------------|
| | | | | |
| 1 | | 1 : 1 : 0 | 6 | 0 |
| 2 | | 1 : 0.5 : 0.6 | 6 | 85 (64) |
| 3 | | 1 : 1 : 0 | 6 | 0 |
| 4 | | 1 : 0.5 : 0.6 | 6 | 56 (33) |
| 5 | | 1 : 0.5 : 0.6 | 18 | 86 (70) |
| 6 | | 1 : 1 : 1 | 6 | 83 (69) ^c |
| 7 | | 1 : 0.5 : 0.6 | 18 | 33 (18) |
| 8 | | 1 : 1 : 1 | 18 | 66 (33) |
| 9 | | 1 : 0.5 : 0.6 | 19 | 0 |
| 10 | | 1 : 1 : 1 | 19 | 0 |
| 11 | | 1 : 0.5 : 0.6 | 6 | 90 (69) |
| 12 | | 1 : 0.7 : 0.7 | 7 | 100 (82) |
| 13 | | 1 : 0.5 : 0.6 | 6 | 65 (43) |
| 14 | | 1 : 0.7 : 0.7 | 7 | 95 (72) |
| 15 | | 1 : 0.5 : 0.6 | 13 | 13 (7) |

^a Molar ratio of substrate : I₂ : H₂O₂; ^b First number represents conversion determined from ¹H NMR spectra of the crude reaction mixture; the bracketed number corresponds to isolated yield; ^c 5% of diiodinated product also present

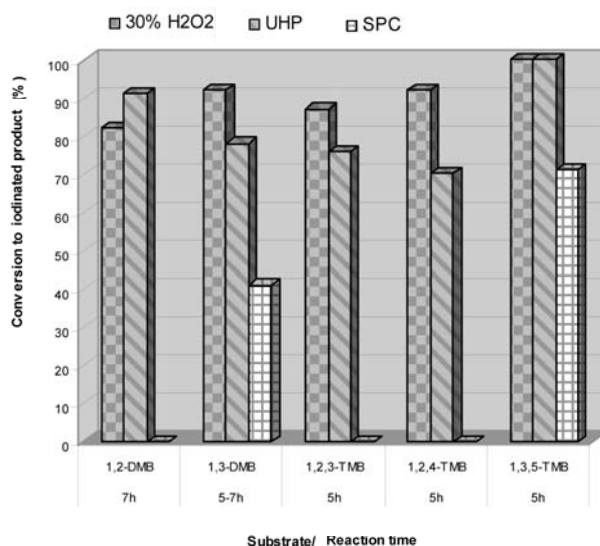
while in the case of 1,4-dimethoxy benzene (**3**) no transformation occurred (Entries 4–6, Table 1) and only starting material was present in the reaction mixture, even after 23 h of reaction at 45 °C with the ratio of substrate : I₂ : H₂O₂ corresponding to 1 : 1 : 1. Similar observations were noticed in our previous experience, where the solid form of H₂O₂, namely urea-H₂O₂, was investigated as an oxidant and/or mediator of iodination under solvent-free conditions.^{9c} Except for 1,4-dimethoxy benzene (**3**), the results shown in Table 1 are also in accordance with conclusions on iodination using water as a reaction medium and 30% aq. H₂O₂ as an oxidiser. Under SFRC iodo-functionalisation through ion-radical formation does not seem to be favourable, while in water the formation of ion-radicals was assumed to be possible.^{12f}

Furtheron, alkyl aryl ketones were chosen as substrates of interest to study the regioselectivity of iodo-functionalisation under SFRC with I₂ in the presence of 30% aq. H₂O₂ as the oxidant and mediator of iodination. It is known that in the case of F-TEDA-BF₄ as a mediator of iodination, the regioselectivity of iodine introduction into alkyl aryl ketones can be regulated by the choice of solvent.¹⁵ However, in the case of 30% aq. H₂O₂ as the oxidant, for reactions in solvents, iodine was introduced in the alkyl chain at the α -position to the carbonyl group.^{12c,12f} Transformation of acetophenone derivatives using the reagent system I₂/30% H₂O₂ was investigated under SFRC. Blank experiments, performed in a way that only the substrate was heated at 45 °C with I₂ and without any oxidant and organic solvent, showed either very low conversion of starting material or no reaction at all after 6 hours heating (entries 1, 3, Table 2). On the other hand, the presence of 30% H₂O₂ promoted the introduction of iodine at the alkyl position of acetophenone **7** (Entry 2, Table 2). Iodine was also introduced at the alkyl position in the cases of substrates possessing an activated aromatic ring. 4-Methoxy acetophenone (**8**) and 3,4-dimethoxy acetophenone (**9**) were thus transformed to their α -iodo substituted derivatives, but no iodinated product was obtained when 3,4,5-trimethoxy acetophenone (**10**) was reacted with the I₂/30% H₂O₂ reagent system for 19 h at 45 °C. A ratio of substrate : I₂ : H₂O₂ corresponding to 1 : 0.5 : 0.6 under SFRC was sufficient for iodine atom introduction with high yield for unsubstituted acetophenone (**7**) after 6 hours, and 4-methoxy acetophenone (**8**) after 18 hours heating at 45 °C, while for dimethoxy-substituted acetophenone analogue (**9**), a 1 : 1 : 1 ratio of substrate : I₂ : H₂O₂ was necessary for efficient transformation. In the first case, the atom economy principle was followed, and highlights H₂O₂ in the role of an activator and an oxidiser, thus enabling the regeneration of iodine after the first electrophilic attack. In the latter case, H₂O₂ plays only the role of an activator of the iodinating system. As a consequence, it requires one whole molar equivalent of the reagent and lacks the atom economy aspect in regard to iodine.

Additionally, the effect of ketone structure for iodination was also investigated on cyclic alkyl aromatic ketones under SFRC using I₂ and 30% H₂O₂. The introduction of iodine proved to be efficient for 1-indanone (**11**) and 1-tetralone (**12**) with 0.5 molar equivalent of the reagent system after heating at 45 °C, thus obeying the atom economy principle in respect to iodine. Even higher yields were achieved when the amount of reagent was raised to 0.7 molar equivalents. These results are similar to those when the urea-H₂O₂ complex was used as a solid form of oxidiser.^{9c} Addition of a methoxy group to the aromatic ring dramatically affected the outcome of the reaction. In the case of 4-methoxy-1-indanone, no conversion occurred with 0.5 molar equivalent of the reagent after 7 h at 45 °C, while in the case of 5-methoxy-1-indanone (**13**) the conversion was barely 13%.

Finally, attempts were made to iodinate methoxy substituted benzaldehydes with I₂/30% H₂O₂ under SFRC. After 18 hours at 45 °C only starting materials were present in the reaction mixture, regardless of the amount of reagent used.

A comparison of the efficiency of different forms of hydrogen peroxide as an oxidiser and/or a mediator of iodination SFRC is shown on Figure 1. As can be seen, 30% aq. H₂O₂ and solid urea-H₂O₂ (UHP) proved to be far superior in comparison to sodium percarbonate (SPC), whose efficiency was moderate in the case of most activated substrates, namely 1,3-dimethoxy benzene (**2**) and 1,3,5-trimethoxy benzene (**6**), while it was negligible for all other substrates. 30% H₂O₂ and the urea-H₂O₂ adduct sho-



DMB is dimethoxy benzene, TMB is trimethoxy benzene

Figure 1: The effect of different forms of H₂O₂ on the efficiency of the introduction of an iodine atom into dimethoxy- and trimethoxy benzenes^a

^a) Reaction conditions: substrate (1 mmol), I₂ (0.5 mmol; 1.0 mmol in the case of 1,2-DMB), H₂O₂ (0.6 mmol; 1.0 mmol in the case of 1,2-DMB), 45 °C.

wed similar efficiency as mediators of iodination under SFRC, with the former of a slightly better performer at 1 : 0.5 : 0.6 ratio of substrate : I₂ : H₂O₂ in the case of 1,3-dimethoxy benzene (**2**), 1,2,3-trimethoxy benzene (**4**) and 1,2,4-trimethoxy benzene (**5**), while the latter was slightly more efficient in the case of 1,2-dimethoxy benzene (**1**) but with a whole molar equivalent of the iodinating reagent.

The present results on the introduction of an iodine atom into organic compounds performed under SFRC and the same reactions performed in water,^{12f, 12g} were comparatively evaluated for 30% H₂O₂-mediated iodination. These comparisons are depicted on Figure 2. Both reaction conditions gave similarly high conversions for substrates, requiring 0.5 molar equivalent of reagent for efficient iodotransformation and following the atom economy principle. A remarkable difference was noted for 1,4-dimethoxy benzene (**3**), which after 27 h at 50 °C using 1 : 1 : 1 ratio of substrate : I₂ : H₂O₂ was 94% converted to 2-iodo-1,4-dimethoxy benzene (**3a**) in water, while after treatment under SFRC for 23 hours at 45 °C with the same ratio of substrate : I₂ : H₂O₂ only starting material was isolated. It is well-known that the reactivity of 1,4-dimethoxy benzene in solvents is regulated by the formation of cation-radical intermediate,¹³ which might explain the exceptional difference in reactivity for this substrate in water and under SFRC.

Furthermore, different forms of H₂O₂ as oxidant and the required ratio of substrate : I₂ : oxidant for the most efficiently mediated iodo-transformation were evaluated for alkyl aryl ketones. The results are gathered in Table 3. As was the case for dimethoxy- and trimethoxybenzenes, sodium percarbonate again proved to be only poorly or even negligibly efficient oxidant under solvent-free reaction

conditions. Significantly more efficient under the same reaction conditions were 30% aq. H₂O₂ or urea-H₂O₂ complex as mediators of iodination. For 1-indanone (**11**) and 1-tetralone (**12**) a 1 : 0.5 : 0.6 ratio of substrate : I₂ : oxidant was sufficient for introduction of an iodine atom into the alkyl position next to the carbonyl group. Both oxidants were of similar efficiency in the case of 1-tetralone (**12**), while UHP showed superiority in terms of efficiency in the case of 1-indanone (**11**). As regards acetophenones, the required amount of reagent and more suitable form of H₂O₂ for the most efficient iodo-transformation cannot be easily deduced inferred from the structure of the substrate. As can be seen from Table 3, 0.5 molar equivalent of reagent was sufficient for unsubstituted acetophenone (**7**) when 30% aq. H₂O₂ was used as oxidant, while in the case of UHP, a 1 : 1 : 1 molar ratio of substrate : I₂ : UHP showed considerably better result. For 4-methoxy acetophenone (**8**) a 1 : 1 : 1 ratio was more favourable for both 30% H₂O₂ and UHP after 6h at 45 °C under SFRC; however high conversion was also achieved with only 0.5 molar equivalent of reagent in the case of 30% H₂O₂ mediated iodofunctionalisation after prolonging the reaction time to 18h. In the case of 3,4-dimethoxy acetophenone (**9**), a 1 : 1 : 1 ratio of substrate : I₂ : oxidant yielded better conversion than in the case of 30% H₂O₂ as an oxidant, while the UHP-mediated reaction showed almost no difference in regard to the amount of reagent used. Though 3,4,5-trimethoxy acetophenone (**10**) was transformed to iodinated product in a fairly low yield by the use of UHP as oxidant, a 1 molar equivalent of reagent was preferred, while the 30% H₂O₂-mediated reaction gave no iodinated product. To sum up, reactions following the atom economy principle in regard to iodine in 30% H₂O₂-mediated iodination were valid for 1-indanone (**11**), 1-tetralone

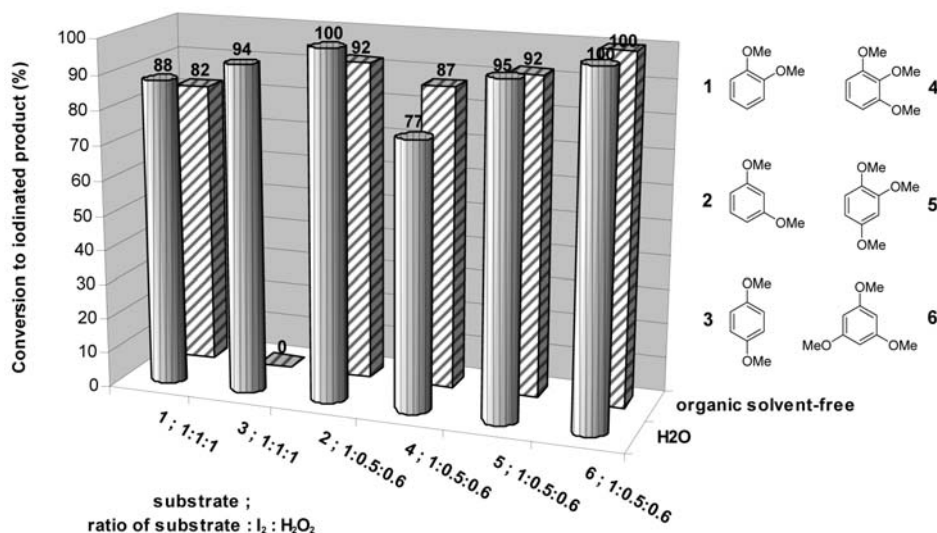
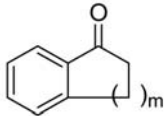

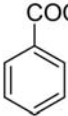
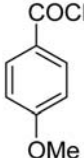
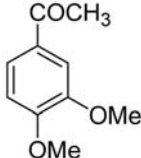
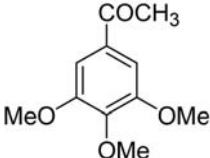


Figure 2: The effect of reaction conditions on the iodination of dimethoxy- and trimethoxy benzenes mediated by 30% H₂O₂.^a

^a Reaction conditions: reaction temperature: 45 °C, reaction time: **1** 18h; **2** 5h; **3** 27 h; **4**, **5** and **6** 5h;

Table 3: Efficiency of different forms of H₂O₂ for introduction of an iodine atom into the alkyl position of alkyl aryl ketones under SFRC

| Substrate |  | |  | |  | |  | |  | |  | |
|---|---|------|---|------|---|-------------------|---|-------|---|-------|---|--|
| | 11 | 12 | 7 | 8 | 9 | 10 | | | | | | |
| | m = 1 | | m = 2 | | Conversion ^a (reaction time) | | | | | | | |
| Ratio ^b S:I ₂ : [O] | A | | A | | B | | A | | B | | A | |
| 30% H ₂ O ₂ | 65% | 90% | 85% | | 56% | 83% | 33% | 66% | 0 | 0 | | |
| | (6h) | (6h) | (6h) | | (6h) | (6h) ^c | (18h) | (18h) | (19h) | (19h) | | |
| | | | | | 86% | | | | | | | |
| | | | | | (18h) | | | | | | | |
| UHP | 80% | 90% | 64% | 89% | 48% | 79% | 46% | 47% | 24% | 34% | | |
| | (5h) | (6h) | (6h) | (6h) | (6h) | (6h) | (6h) | (6h) | (17h) | (17h) | | |
| SPC | 2% | 30% | 0 | | 0 | | 0 | 0 | 5 | 10 | | |
| | (7h) | (7h) | (7h) | | (7h) | | (18h) | (18h) | (19h) | (19h) | | |

^a Conversion determined from ¹H NMR spectra; ^b Ratio of substrate:I₂:oxidant corresponding to 1:0.5:0.6 denoted as A and 1:1:1 denoted as B; UHP is urea-H₂O₂ adduct, SPC is sodium percarbonate (2Na₂CO₃·3H₂O₂). ^c also 9% diiodinated product present in the crude reaction mixture

(12), acetophenone (7) and 4-methoxy acetophenone (8), while a 1 : 1 : 1 ratio of substrate : I₂ : H₂O₂ was required for 3,4-dimethoxy acetophenone (9). On the other hand, the atom economy principle was not followed in UHP-mediated solvent-free reactions in the case of acetophenones, but it was achieved in the case of cyclic aryl alkyl ketones, namely 1-indanone (11) and 1-tetralone (12).

3. Conclusions

Iodine was efficiently introduced into several methoxy-substituted benzene derivatives and alkyl aryl ketones with 30% H₂O₂ as oxidant and without the presence of an organic solvent or any metal or acid catalysts. Alkyl aryl ketones were iodinated regioselectively at the alkyl position next to the carbonyl group. High atom economy in regard to iodine was achieved in cases where a 1 : 0.5 : 0.6 ratio of substrate : I₂ : H₂O₂ was sufficient for the most efficient transformation to iodinated product, which was the case for 1,3-dimethoxy benzene (2), 1,2,3-trimethoxy benzene (4), 1,2,4-trimethoxy benzene (5), 1,3,5-trimethoxy benzene (6), acetophenone (7), 4-methoxy acetophenone (8), 1-indanone (11) and 1-tetralone (12). In these cases iodotransformation proceeds through an ionic mechanism and H₂O₂ plays the role of an activator of the iodinating system and regenerator of iodide released during the process. The iodide ion liberated after initial electrophilic attack of iodine is oxidised by H₂O₂ in the second stage, thus providing regenerated iodine for a second electrophilic attack on the substrate. In cases where the required ratio of substrate : I₂ : H₂O₂ for the most efficient iodo-

transformation corresponds to 1 : 1 : 1, H₂O₂ is believed to play only the role of an activator of the iodinating system. In such a way 1,2-dimethoxy benzene (1), 3,4-dimethoxy acetophenone (9) and 3,4,5-trimethoxy acetophenone (10) were iodinated, while under the same reaction conditions the iodination of 1,4-dimethoxy benzene (3) failed, contrary to the outcome of the reaction performed in water as reaction medium under otherwise similar conditions. A comparative evaluation of different forms of H₂O₂ as oxidant and mediator of iodination under SFRC, revealed the significant superiority of 30% aq. H₂O₂ and solid urea-H₂O₂ to sodium percarbonate (solid). 30% H₂O₂ and urea-H₂O₂ showed similar performances in terms of efficiency, with slightly better preference given to 30% H₂O₂ in the case of trimethoxy substituted benzenes (4, 5, 6) and 1,3-dimethoxy benzene (2). Taking into account that H₂O is the only side product of oxidation using H₂O₂, while in the case of UHP urea also remains after the release of hydrogen peroxide, 30% aq. H₂O₂ is considered more advantageous as a mediator of iodination. Such a straightforward conclusion cannot be derived for alkyl aryl ketones since the required amount of reagent for the most efficient transformation seems to depend heavily on the structure of the substrate as well as the oxidant. However, UHP performed better in the case of 1-indanone (11) requiring 0.5 molar equivalent of reagent, while for acetophenones (7, 8, 9) 30% H₂O₂-mediated reactions were more efficient, except in the case of 3,4,5-trimethoxy acetophenone (10).

In addition, we would like to emphasize the environmentally friendlier approach of these iodotransformations compared to conventional methods. Avoiding the use of organic solvents for performing reactions, the use of a

non-toxic, relatively cheap, safe and stable oxidant, with its benign by-product of oxidation, the atom economy achieved in many cases, together with the general mildness and simplicity of a method should be stressed.

4. Experimental

Iodine and substrates were purchased from Sigma Aldrich. Iodine and solid substrates were finely powdered in a mortar before use, while liquid substrates were used as received. 30% aq. 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 amount of KI, the amount of iodine released was calculated based on titration with $\text{Na}_2\text{S}_2\text{O}_3$. *t*-BuOMe was purchased from Riedel-de-Haën, other chemicals (anhydrous Na_2SO_4 and $\text{Na}_2\text{S}_2\text{O}_3$) from Merck and were used as received. Mps were determined on a Büchi apparatus. ^1H 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.

4. 1. General Procedure

Finely powdered iodine (127 mg, 0.5 mmol; 254 mg, 1 mmol) was added to neat liquid substrate (1 mmol) or finely powdered substrate in the case of solid compounds. The mixture was vigorously shaken in order to obtain a good distribution between substrate and iodine molecules in a 5-mL round-bottom flask. Pulverisation of solid compounds was made in a mortar prior to their transfer to the 5-mL round bottom-flask. 30% aq. H_2O_2 containing 0.6 mmol (20.4 mg) or 1 mmol (34 mg) of active H_2O_2 was added. Reactions were carried out at 45 °C for various times (see Tables 1, 2). Since the experiments were performed on a small scale, products were extracted with *t*-BuOMe (10 mL) to ease their isolation. The organic phase was washed with an aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (10%, 20 mL) in order to destroy unreacted iodine, H_2O (10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixtures were analysed by TLC, ^1H NMR and mass spectroscopy and products identified on the basis of comparison with their known spectroscopic data.¹⁶ Yields of iodinated products are listed in Tables 1–3.

In order to demonstrate that a solvent can be completely omitted, both for reaction performance and during the isolation step, two representative experiments illustrating the isolation approach to products of different aggregate state were performed on a gram scale. 1,3-dimethoxy

benzene (**2**) was chosen as a liquid substrate which provides a liquid iodinated product (**2a**) and solid 1,3,5-trimethoxy benzene (**6**) which yields solid product **6a**.

4. 2. Iodination of 1,3-dimethoxy Benzene (**2**) on the Gram Scale

Finely powdered iodine (1.27 g, 5 mmol) was added to 1,3-dimethoxy benzene **2** (10mmol, 1.38 g), followed by addition of 30% aq. H_2O_2 (0.68g, 6 mmol of active H_2O_2). After 5 h of stirring at 45 °C, an aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (10%, 30 mL) was added and vigorously stirred in order to destroy unreacted iodine. Separation of the aqueous layer from the organic product was made in a separatory funnel and 2.38g (90%) of oily organic material identified as crude 4-iodo-1,3-dimethoxy benzene (**2a**)^{16a} was isolated.

4. 3. Iodination of 1,3,5-trimethoxy Benzene (**6**) on Gram Scale

Prior to the reaction, the substrate and iodine were finely triturated in a mortar, after which both were transferred to a 5-mL round-bottom flask. To the mixture of finely powdered substrate **6** (0.84g, 5 mmol) and iodine (0.635g, 2.5 mmol), 30% aq. H_2O_2 containing 3 mmol (0.102g) of active H_2O_2 was added. After 18 h heating at 45 °C the reaction mixture was stirred with an aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (10%, 50 mL) in order to destroy unreacted iodine. Filtration under reduced pressure gave 1.348g (91%) of solid material, crystallised from $\text{CH}_2\text{Cl}_2/\text{MeOH}$ and identified as 2-iodo-1,3,5-trimethoxy benzene (**6a**, 88%; mp = 120-122 °C)^{16a}.

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Povzetek

Elementarni jod ob prisotnosti 30% vodne raztopine vodikovega peroksida smo uporabili za selektivno jodiranje metoksi substituiranih benzenovih derivatov, acetofenona, 1-indanona in 1-tetralona pod reakcijskimi pogoji brez uporabe topila. Jodiranje di- in trimetoksi benzenovih derivatov je poteklo na aromatsko jedro, medtem ko smo opazili regioselektivno funkcionalizacijo alkilne verige na α -mesto ob karbonilni skupini v primeru aril-alkil ketonov. Vodikov peroksid igra v procesu jodiranja vlogo aktivatorja in regeneratorja joda, v posameznih primerih pa le vlogo aktivatorja, kar se odraža v stehiometriji reakcije. Primerjali smo vpliv posameznih oblik vodikovega peroksida (30% vodna raztopina, urea-H₂O₂ kompleks in natrijev perkarbonat: 3Na₂CO₃ · 3H₂O₂) na učinkovitost jodiranja pod reakcijskimi pogoji brez uporabe topila, v primeru 30% H₂O₂ pa še z rezultati dobljenimi po reakciji v vodnem mediju.