Iodofunctionalized molecules are versatile building blocks in preparative organic chemistry with application, for example, in cross-coupling reactions,\(^\text{1}\) as well as in iodine–lithium\(^\text{2}\) and iodine–magnesium\(^\text{3}\) exchange processes. Furthermore, several organic compounds containing iodine are biologically active substances\(^\text{6}\) or providing well-established strategies to prepare iodinated aromatic and heteroaromatic compounds. Although diazotization–iodination reactions have limitations related to the use of starting materials containing amino groups, and electrophilic iodination reactions employ relatively toxic, oxidizing, and expensive halogenating reagents, both approaches can be considered useful in organic synthesis.\(^\text{10,11}\)

To circumvent the disadvantages, Detty and co-workers have explored halogenation reactions involving halide salts as the sources of halogen and aqueous hydrogen peroxide as a mild oxidizer, and the reactions have been successfully catalyzed by chalcogen-containing compounds.\(^\text{12}\) In these transformations the organochalcogens employed as catalysts mimic haloperoxidase enzymes allowing environmentally friendly halogenations of organic substrates.\(^\text{12,14}\)

Nonetheless, to our knowledge, only one study that provides a general method for the iodination of organic substrates employing NaI and H\(_2\)O\(_2\) catalyzed by a water-soluble organotelluride has been reported.\(^\text{12}\) Only low catalyst loadings were required for the iodinations described; however, the water-soluble catalyst had to be prepared in four steps from 4-N,N-bis(carboethoxymethyl)aniline.\(^\text{12}\) In this context, having in mind the demand for iodinated aromatic and heteroaromatic compounds in synthetic organic chemistry, along with the potential applications of iodinated compounds in medicine, we have developed a novel method for the biomimetic iodination of aromatic and heteroaromatic compounds in water without a co-solvent. The method affords iodinated compounds in isolated yields of 37 to 99%. The catalytic system has potential for the bromination of aromatic substrates.

### Key words
biomimetic synthesis, iodofunctionalization, selenium catalysis, iodination, aqueous reaction

### Abstract
A biomimetic iodofunctionalization of aromatic and heteroaromatic compounds has been developed using NaI as a source of iodine and 30% \(\text{H}_2\text{O}_2\) as a mild oxidant, as well as SeCl\(_4\) as a commercially available catalyst in water without a co-solvent. The method affords iodinated compounds in isolated yields of 37 to 99%. The catalytic system has potential for the bromination of aromatic substrates.

Iodofunctionalized aromatic or heteroaromatic substrates employing NaI and \(\text{H}_2\text{O}_2\) catalyzed by a water-soluble organotelluride has been reported.\(^\text{12}\) Only low catalyst loadings were required for the iodinations described; however, the water-soluble catalyst had to be prepared in four steps from 4-N,N-bis(carboethoxymethyl)aniline.\(^\text{12}\) In this context, having in mind the demand for iodinated aromatic and heteroaromatic compounds in synthetic organic chemistry, along with the potential applications of iodinated compounds in medicine, we have developed a novel method for the biomimetic iodination of aromatic and heteroaromatic compounds in water without a co-solvent. The method affords iodinated aromatic and heteroaromatic compounds in good isolated yields. Through this methodology we can avoid the limitations related to the use of starting materials containing amino groups, as well as oxidizing, and expensive halogenating reagents, with the convenience of employing SeCl\(_4\) as a commercially available catalyst.
Initially, the reactions were carried out employing 1-(4-hydroxyphenyl)ethanone (1a), NaI (2.5 equiv), 30% aqueous H₂O₂ (0 to 5 equiv), the appropriate catalyst (0 to 20 mol%), and distilled water. The mixtures were stirred at room temperature or 50 °C for 24 h or 48 h (Table 1, entries 1–11; Procedure A). The use of selenium and tellurium powder was evaluated, envisioning the in situ formation of the corresponding selenium(IV) and tellurium(IV) species, which could catalyze the reaction. However, in both experiments, 1-(4-hydroxy-3-iodophenyl)ethanone (3) was obtained in yields lower than 5% (entries 1 and 2). When the transformation was performed in the presence of SeCl₄ (5 mol%) or TeCl₄ (5 mol%), we obtained 3 in yields of 20% and 21%, respectively (entries 3 and 4). In the absence of catalyst, compound 3 was isolated in 10% yield (entry 5). At this point, we decided to continue the experiments using SeCl₄ as catalyst based on the cost-benefit ratio. The use of distilled water instead of a buffer solution was reasonable because the reactions presented initial and final pH values of 6 (entries 1–5). Allowing the reaction to proceed in the absence of 30% H₂O₂, we did not observe the formation of 1-(4-hydroxy-3,5-diiodophenyl)ethanone (2a) or 3. In addition, both initial and final pH values were pH 4 (entry 6). Increasing the catalyst loading to 20 mol% and the reaction time to 48 h, compounds 2a and 3 were obtained in yields of 38% and 23%, respectively (entries 7–9). Through an increase of reaction temperature, we isolated compounds 2a and 3 in yields of 37% and 26%, respectively (entries 10 and 11). The reactions outlined in entries 7–10 presented initial and final pH values of 6. Interestingly, when the transformation was performed at 50 °C for 48 h, the initial pH value was 6 and the final pH value was 1 (entry 11).

In an attempt to increase the yield of compound 2a, the reactions were carried out by preparing a solution of 1a in distilled water, which was subjected to stirring at room temperature or 50 °C. Then, a solution containing SeCl₄ (20 mol%) in distilled water was added. Afterwards, 2 M aqueous solutions of NaI (2.5 equiv) and of H₂O₂ (5 equiv) were added alternately to the mixture in small aliquots (every 5 min over a period of 50 min). The resulting mixture was

![Table 1](image-url)
maintained under stirring at room temperature or 50 °C for 3 h, 24 h or 48 h (Table 1, entries 12–16; Procedure B). By employing Procedure B, at room temperature for 3 h, 2a and 3 were isolated in yields of 57% and <5%, respectively (entry 12). On increasing the reaction time to 24 h, and then to 48 h, compounds 2a and 3 were obtained in yields of 59–62% and 23–27%, respectively (entries 13 and 14). When the transformation was carried out at 50 °C for 24 h or 48 h, the products 2a and 3 were isolated in similar yields of 62% and 26%, respectively (entries 15 and 16). All reactions performed using Procedure B presented initial and final pH values of 6 (entries 12–16).

By employing the optimal conditions, i.e., the conditions that promoted the highest incorporation of iodine into 1a (Table 1, entry 15), we examined the scope of the transformation using phenols, anilines, and pyrazoles (1a–o) with electron-donating and electron-withdrawing groups (Table 2).15 By performing the reaction with phenolic compounds containing electron-withdrawing groups (1a–c), we obtained the diiodinated products 2a–c in yields from 54% to 90% (entries 1–3). The relatively low yield achieved for compound 2b (entry 2) was tentatively attributed to hydrolysis of the cyano group under the reaction conditions. However, no experimental evidence was obtained to support such a proposal. When 4-methylphenol (1d) was subjected to the diiodination reaction, 2,6-diiodo-4-methylphenol (2d) was isolated in 30% yield (entry 4). The optimized reaction conditions did not work as expected for phenolic compounds containing electron-donating groups. By reducing the amounts of NaI and H₂O₂ to 1.25 equiv and 2.5 equiv, respectively, di- and monohalogenated phenols (1e–g) provided moniodinated products (2e–g) in yields from 57% to 76% (entries 5–7). Likewise, the anilines 1h–j led to the formation of moniodinated anilines (2h–j) in isolated yields from 71% to 92% (entries 8–10). When pyrazole (1k) was treated with NaI (1.25 equiv) and H₂O₂ (2.5 equiv) in the presence of SeCl₄ (20 mol%) using distilled water as solvent at 50 °C for 24 h, 4-iodopyrazole (2k) was obtained in 25% yield (entry 11). In this reaction the starting material 1k was partially recovered and unidentified by-products were produced according to GC/MS analysis. By increasing the amounts of NaI (2.5 equiv), H₂O₂ (5 equiv), and SeCl₄ (40 mol%), we isolated 4-iodopyrazole (2k) in 37% yield (entry 11). Treatment of 3,5-dimethylpyrazole (1l) with NaI (1.25 equiv), H₂O₂ (2.5 equiv), and SeCl₄ (20 mol%) gave 4-iodo-3,5-dimethylpyrazole (2l) in 99% yield (entry 12). Similarly, when 1-phenylpyrazole (1m) was subjected to the monoiodination reaction, 4-iodo-1-phenylpyrazole (2m) was isolated in 65% yield (entry 13). The iodination reaction of 3-amino-1,5-dimethylpyrazole (1n) provided the moniodinated product 2n in 75% yield (entry 14). Conversely, when 1,5-dimethyl-1H-pyrazole-3-carboxylic acid (1o) was subjected to the iodination reaction, 4-iodo-1,5-dimethyl-1H-pyrazole-3-carboxylic acid (2o) was not obtained, the starting material 1o was partially recovered, and unidentified substances were produced according to GC/MS analysis (entry 15).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aromatic compound 1</th>
<th>Iodinated aromatic compound 2</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a</td>
<td>62 (44)</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>2b</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>2c</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>2d</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>1e Br</td>
<td>2e Br</td>
<td>76</td>
</tr>
</tbody>
</table>
A reasonable catalytic cycle to provide iodinated compounds 2 commences with hydrolysis of SeCl₄ leading to Se(OH)₄. After that, intermediates A and B are produced through ligand exchange reactions. Then, intermediate B undergoes reductive elimination, affording molecular iodine and Se(OH)₂, which, in the presence of hydrogen...
peroxide, regenerates Se(OH)$_4$. The incorporation of iodine into aromatic and heteroaromatic compounds 1 takes place via electrophilic iodination (Scheme 1).

![Scheme 1](image)

Scheme 1 Catalytic cycle proposed for the iodination reaction of compounds 1

We carried out the treatment of 1a with NaI (2.5 equiv) and H$_2$O$_2$ (5 equiv) using SeCl$_4$ (20 mol%) in water at 50 °C for 24 h (Table 1, entry 15) to conduct analyses of the reaction medium by electrospray ionization mass spectrometry (ESI-MS), employing positive (ESI+) and negative (ESI−) modes, aiming to identify transient species related to the catalytic cycle of Scheme 1, as well as to follow the transformation progress at 1, 3, 6, 12, and 24 hours. However, no transient species related to the catalytic cycle of Scheme 1 were detected.

In an attempt to provide some experimental support for the catalytic cycle shown in Scheme 1, we performed qualitative tests aiming to confirm the formation of molecular iodine in the reaction medium. Accordingly, we prepared aqueous solutions of SeCl$_4$ (0.08 M) and of NaI (2 M). Then, by addition of 2.5 mL of NaI (2 M) to 5 mL of SeCl$_4$ (0.08 M), both colorless solutions produced a brownish mixture, indicating a possible formation of molecular iodine; this conclusion was supported by addition of a solution of starch (1%; 5 mL), which produced a black mixture. In addition, another test was performed, in which we prepared the brownish solution (as described above) and added a saturated solution of Na$_2$S$_2$O$_3$ (5 mL) leading to a colorless aqueous solution presumably by reduction of molecular iodine back to iodide.

Aiming to expand the scope of the developed transformation (Table 2), we considered the use of NaBr and NaCl for the introduction of Br and Cl atoms, respectively, in aromatic and heteroaromatic compounds 1. Thus, we treated 1a with NaBr (2.5 equiv) and H$_2$O$_2$ (5 equiv) using SeCl$_4$ (20 mol%) in water at 50 °C for 24 h and obtained 1-(3,5-dibromo-4-hydroxyphenyl)ethanone (4) in 62% yield (Scheme 2).

![Scheme 2](image)

Scheme 2 Dibromination reaction of compound 1a

Allowing 1a to react with NaCl (2.5 equiv) and H$_2$O$_2$ (5 equiv) employing SeCl$_4$ (20 mol%) in water at 50 °C for 24 h, 1-(3,5-dichloro-4-hydroxyphenyl)ethanone (5) was not obtained. Instead, the starting material 1a was partially recovered, and unidentified substances were produced according to GC/MS analysis. It is worth mentioning that, in the case of the reaction using NaCl, the pH remained between 0 and 1 throughout the reaction (Scheme 3).

![Scheme 3](image)

Scheme 3 Dichlorination reaction of compound 1a

The structures proposed for compounds 2a–n, 3, and 4 are supported by their $^1$H and $^{13}$C NMR, IR, and mass spectra (see the Supporting Information).

In summary, a biomimetic iodofunctionalization of aromatic and heteroaromatic compounds has been developed that employs NaI as an inexpensive iodine source, 30% H$_2$O$_2$ as a mild oxidizing agent, and SeCl$_4$ as a commercially available catalyst, in water without a co-solvent, affording iodinated aromatic and heteroaromatic compounds in good isolated yields. The method can be considered an attractive alternative approach to prepare iodinated compounds, with potential applications in organic synthesis, medicinal chemistry, and medicine. In addition, the catalytic system developed presents potential for the bromination of aromatic and heteroaromatic compounds. In this sense, we intend to explore the bromination of aromatic and heteroaromatic substances and the results will be disclosed in due course.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690337.
References and Notes


(15) Preparation of Iodinated Compounds 2a–n and 3: General Procedure: To a solution of compound 1a–o (2 mmol in 2.5 mL of H2O) under stirring at 50 °C was added a solution of Sc(i) (20 mmol in 5 mL of H2O). Then, 2 M aqueous solutions of NaI (5 or 2.5 mmol) and of H2O (10 or 5 mmol) were added alternately in small aliquots (every 5 min over a period of 50 min) and the mixture was maintained under stirring at 50 °C for 24 h. A saturated aqueous solution of Na2S2O3 (10 mL) was then added to the reaction, the mixture was extracted with ethyl acetate (3 × 20 mL) and the organic phase was dried over MgSO4. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using an appropriate eluent, to afford the desired product 2a–n and 3.

1-(4-Hydroxy-3,5-diiodophenyl)ethenone (2a): Yield: 483 mg (62%); off-white solid; Rf = 0.55 (CH2Cl2); mp 173 °C [lit.173 °C]. 1H NMR (300 MHz, DMSO-d6); δ = 8.26 (s, 2 H), 3.38 (s, 1 H), 2.51 (s, 3 H). 13C NMR (75 MHz, DMSO-d6); δ = 154.7, 159.8, 139.7, 132.8, 86.4, 26.6. IR (KBr): 3402, 1665, 1460, 1393, 1323 cm–1. MS (EI): m/z (%) = 387.7 (71.7), 372.7 (100.0), 217.8 (401). (j) Lulinski, P.; Kryska, A.; Sosnowski, M.; Skulsli, S. Synthesis 2004, 4411. (k) Barluenga, J. Pure Appl. Chem. 1999, 71, 431.
