An environmentally benign and selective electrochemical oxidation of sulfides and thiols in a continuous-flow microreactor

Citation for published version (APA):

DOI:
10.1039/c7gc01973d

Document status and date:
Published: 07/08/2017

Document Version:
Typeset version in publisher’s lay-out, without final page, issue and volume numbers

Please check the document version of this publication:
• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license above, please follow below link for the End User Agreement:
www.tue.nl/taverne

Take down policy
If you believe that this document breaches copyright please contact us at:
openaccess@tue.nl
providing details and we will investigate your claim.

Download date: 17. Aug. 2019
An environmentally benign and selective electrochemical oxidation of sulfides and thiols in a continuous-flow microreactor

Gabriele Laudadio, Natan J. W. Straathof, Menno D. Lanting, Benny Knoops, Volker Hessel and Timothy Noël*

A practical and environmentally benign electrochemical oxidation of thioethers and thiols in a commercially-available continuous-flow microreactor is presented.

Please check this proof carefully. Our staff will not read it in detail after you have returned it.

Proof corrections must be returned as a single set of corrections, approved by all co-authors. No further corrections can be made after you have submitted your proof corrections as we will publish your article online as soon as possible after they are received.

Please ensure that:

• The spelling and format of all author names and affiliations are checked carefully. Names will be indexed and cited as shown on the proof, so these must be correct.
• Any funding bodies have been acknowledged appropriately.
• All of the editor’s queries are answered.
• Any necessary attachments, such as updated images or ESI files, are provided.

Translation errors between word-processor files and typesetting systems can occur so the whole proof needs to be read. Please pay particular attention to: tables; equations; numerical data; figures and graphics; and references.

Please send your corrections preferably as a copy of the proof PDF with electronic notes attached or alternatively as a list of corrections – do not change the text within the PDF file or send a revised manuscript. Corrections at this stage should be minor and not involve extensive changes.

Please return your final corrections, where possible within 48 hours of receipt, by e-mail to: green@rsc.org. If you require more time, please notify us by email.
**Funder information**

Providing accurate funding information will enable us to help you comply with your funders’ reporting mandates. Clear acknowledgement of funder support is an important consideration in funding evaluation and can increase your chances of securing funding in the future. We work closely with Crossref to make your research discoverable through the Funding Data search tool (http://search.crossref.org/fundref).

Further information on how to acknowledge your funders can be found on our webpage (http://rsc.li/ funding-info).

**What is Funding Data?**

Funding Data (http://www.crossref.org/fundingdata/) provides a reliable way to track the impact of the work that funders support. We collect funding information from our authors and match this information to funders listed in the Open Funder Registry. Once an article has been matched to its funders, it is discoverable through Crossref’s search interface.

**PubMed Central**

Accurate funder information will also help us identify articles that are mandated to be deposited in PubMed Central (PMC) and deposit these on your behalf.

**Providing funder information**

We have included the funder information you gave us on submission in the table below. The ‘Funder name’ shown and their associated ‘Funder ID’ number is written as listed in the Open Funder Registry. **Please check that the funder names and grant numbers in the table are correct.** The funder information should match your acknowledgements. This table will not be included in your final PDF but we will share the data with Crossref so that your article can be found via the Funding Data search tool.

<table>
<thead>
<tr>
<th>Funder name</th>
<th>Funder ID (from the Open Funder Registry)</th>
<th>Award/grant/contract number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Award/grant/contract number</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If a funding organisation you included on submission of your article is not currently listed in the registry it will not appear in the table above. We can only deposit data if funders are already listed in the Open Funder Registry, but we will pass all funding information on to Crossref so that additional funders can be included in future.

**Researcher information**

If any authors have ORCID or ResearcherID details that are not listed below, please provide these with your proof corrections. Please check that the ORCID and ResearcherID details listed below have been assigned to the correct author. Please use this space to add your own unique ORCID iDs and not another researcher’s, as errors will delay publication.

Please also update your account on our online manuscript submission system to add your ORCID details, which will then be automatically included in all future submissions. See here for step-by-step instructions and more information on author identifiers.

<table>
<thead>
<tr>
<th>First (given) name(s)</th>
<th>Last (family) name(s)</th>
<th>ResearcherID</th>
<th>ORCID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabriele</td>
<td>Laudadio</td>
<td></td>
<td>0000-0002-2749-8393</td>
</tr>
<tr>
<td>Natan J. W.</td>
<td>Straathof</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menno D.</td>
<td>Lanting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benny</td>
<td>Knoops</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volker</td>
<td>Hessel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timothy</td>
<td>Noél</td>
<td></td>
<td>0000-0002-3107-6927</td>
</tr>
</tbody>
</table>
Queries for the attention of the authors

Journal: Green Chemistry   Paper: c7gc01973d

Title: An environmentally benign and selective electrochemical oxidation of sulfides and thiols in a continuous-flow microreactor

For your information: You can cite this article before you receive notification of the page numbers by using the following format: (authors), Green Chem., (year), DOI: 10.1039/c7gc01973d.

Editor’s queries are marked like this [Q1, Q2, ...], and for your convenience line numbers are indicated like this [5, 10, 15, ...].

Please ensure that all queries are answered when returning your proof corrections so that publication of your article is not delayed.

<table>
<thead>
<tr>
<th>Query Reference</th>
<th>Query</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>Please carefully check the spelling of all author names. This is important for the correct indexing and future citation of your article. No late corrections can be made.</td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td>Please check that the inserted Graphical Abstract text is suitable. Please ensure that the text fits between the two horizontal lines.</td>
<td></td>
</tr>
<tr>
<td>Q3</td>
<td>Ref. 2c: Please check that the initials are displayed correctly.</td>
<td></td>
</tr>
<tr>
<td>Q4</td>
<td>Ref. 2e, 15a and 17a: Please provide the page (or article) number(s).</td>
<td></td>
</tr>
<tr>
<td>Q5</td>
<td>Ref. 20j and 24: Please provide the name of the patentee(s).</td>
<td></td>
</tr>
</tbody>
</table>
An environmentally benign and selective electrochemical oxidation of sulfi des and thiols in a continuous-flow microreactor†

Gabriele Laudadio, Natan J. W. Straathof, Menno D. Lanting, Benny Knoops, Volker Hessel and Timothy Noël *

A practical and environmentally benign electrochemical oxidation of thioethers and thiols in a commercially-available continuous-flow microreactor is presented. Water is used as the source of oxygen to enable the oxidation process. The oxidation reaction utilizes the same reagents in all scenarios and the selectivity is solely governed by the applied potential. The procedure exhibits a broad scope and good functional group compatibility providing access to various sulfoxides (15 examples), sulfones (15 examples) and disulfides (6 examples). The use of continuous flow allows the optimal reaction parameters (e.g. residence time, applied voltage) to be rapidly assessed, to avoid mass- and heat-transfer limitations and to scale the electrochemistry.

Introduction

Sulfoxide and sulfone moieties are widespread in a broad variety of functional organic molecules. These moieties have been incorporated in numerous pharmaceutical compounds (e.g. Esomeprazole, Dapsone, Sulmazole, Methionine sulfone and Ponazuril) and even in polymeric materials (Fig. 1). Moreover, chiral sulfoxides have been employed as chiral auxiliaries (e.g. Ellman’s sulfinamide, Oppolzer camphorsul tam) and as chiral ligands in asymmetric transition-metal catalyzed transformations (e.g. Skarzewski’s and Hiroi’s ligands, Fig. 1).

Typically, sulfoxides and sulfones can be accessed through oxidation of the corresponding thioether. Hereto, a wide variety of oxidizing agents have been used, such as H2O2 in combination with metal catalysts, m-CPBA, NaIO4, CrO3, KMnO4 and dioxiranes. Unfortunately, these strategies typically suffer from selectivity issues, e.g. overoxidation of the sulfoxide to the sulfone or oxidation of other functional groups within the molecule. And, while hydrogen peroxide is considered to be a green oxidant, its industrial synthesis via the so-called anthraquinone autooxidation process is not sustainable.

Fig. 1. Examples of interesting sulfoxides and sulfones, ranging from pharmaceuticals to chiral ligands.
Oxidation chemistry can also be achieved using alternative and sustainable technologies, such as photochemistry or electrochemistry, which allow to carry out the desired transformation in the absence of strong oxidants. Here, the desired transformation is induced by so-called traceless reagents such as photons or electrons, providing sustainable alternatives for the often hazardous and toxic oxidants.

In addition, these methods are relatively mild and provide good functional group tolerance and high chemoselectivity. Furthermore, sustainable electricity, derived from solar and wind energy, is becoming more abundantly available. Due to the transient nature of these energy sources, small scale electrochemical plants are ideally suited to directly harness this sustainable energy source. Despite the advantages provided by electrochemistry, many organic synthetic practitioners have been discouraged to adopt this technology into their laboratories. This is in part due to the apparent complexity of electrochemical transformations which originates from numerous problems, such as the use of specialized equipment and large amounts of tailor-made electrolytes, mass- and heat-transfer limitations, electrodeposition of organic material on the surface of the electrode and limited scalability. However, many of these challenges can be overcome by combining electrochemistry and continuous-flow microreactor technology. Due to the small dimensions (100 μm–1 mm), micro-flow technology allows to intensify the contact between the reaction mixture and the electrodes, to eliminate mass-transfer limitations and to avoid hot-spot formation. Furthermore, organic deposition on the electrodes can be minimized due to the continuous-flow operation of the reactor.

Using a combination of electrochemistry and continuous-flow microreactors, we questioned whether we could selectively access either the sulfoxide or the sulfone starting from their corresponding thioethers. Specifically, we hoped to develop a set of generally applicable conditions which would allow us to access both compounds simply by tuning the applied potential in the electrochemical flow cell, whilst keeping the reaction mixture the same. This would be a great advance compared to traditional synthetic approaches where each product class requires its own set of conditions with often toxic oxidants, metal catalysts and/or elevated temperatures.

Results and discussion

In order to find the optimal conditions for the direct electrochemical oxidation of thioanisole, the potentiostatic oxidation of thioanisole (1) was taken as a benchmark (Table 1). The Asia Flux reactor was used as a commercially available electrochemical flow module and was equipped with cheap stainless steel electrodes. At the outset of our investigations, it was found that the use of an electrolyte was crucial to maintain a stable current. Optimal results were obtained using tetrabutylammonium perchlorate (TBAClO₄). We also observed that the use of an aqueous acidic solvent was mandatory to lower the pH which allowed to increase the redox potential of the Fe electrodes, as explained by Pourbaix’s diagrams (Table 1, entries 3 and 4). Consequently, the combination of tetrabutylammonium perchlorate in MeCN with aqueous HCl (3 : 1 v/v, 0.1 M HCl in H₂O), applied potential: 2.5 V (2.1 mA cm⁻², Fe anode/cathode, Vₑ_stylesheet: 300 μL), residence time: 5 min (at a flowrate of 0.06 mL min⁻¹).

### Table 1 Optimization of reaction condition for the electrochemical oxidation of sulfides in continuous flow

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from above</th>
<th>Conv. (%)</th>
<th>% 1-A</th>
<th>% 1-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>63</td>
<td>62</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Residence time of 10 min</td>
<td>75</td>
<td>72</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>No H₂O/HCl (0.1 M)</td>
<td>n.r.</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>No electrolyte</td>
<td>n.r.</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>0.2 M H₂O/HCl</td>
<td>37</td>
<td>34</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>No H₂O/HCl, ACN saturated with O₂</td>
<td>39</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Potential at 3.0 V</td>
<td>92</td>
<td>65</td>
<td>27</td>
</tr>
<tr>
<td>8</td>
<td>Potential at 3.5 V</td>
<td>98</td>
<td>59</td>
<td>39</td>
</tr>
<tr>
<td>9</td>
<td>Potential at 4.0 V</td>
<td>99</td>
<td>7</td>
<td>92</td>
</tr>
</tbody>
</table>

Reaction conditions and variations on the electrochemical oxidation of thioanisole. Reagents and conditions: Thioanisole (1 mmol, 0.1 M), TBAClO₄ (0.1 mmol), MeCN/HCl (10 mL, 3 : 1 v/v, with 0.1 M HCl in H₂O), applied potential: 2.5 V (2.1 mA cm⁻², Fe anode/cathode, Vₑ_stylesheet). Further increase in the potential results into a critical oxidation of the [O]-source. Furthermore, in the presence of water, gas formation can be noticed due to water splitting (see ESI†).

With these preliminary results in hand, the effect of the applied potential on the observed selectivity was investigated in greater detail. Hereto, a single sweep voltammetry experiment was performed at a constant residence time of 5 min (Fig. 2A). The polarogram shows a clear plateau at 2.0–2.5 V, which corresponds to the first oxidation step of thioanisole toward 1-A (Fig. 2B). When the applied potential reaches approximately 3.5–4.0 V, another plateau is observed, which corresponds to the second oxidation step (viz 1-A → 1-B or 1 → 1-B). Further increase in the potential results into a critical oxidation of the stainless steel electrodes and should be avoided. It is clear that such polarograms represent a very useful tool to...
establish the optimal reaction conditions to obtain either the sulfoxide or the sulfone from a specific thioether (see Fig. 2B and ESI†).

Next, the effect of flow rate and residence time was investigated (Fig. 3). These investigations were carried out to define the optimal flowrate/residence time ratio in order to avoid mass-transfer limitations. At lower flow rates, mixing is not intense enough to facilitate diffusion of the reactants from the bulk to the electrodes. At higher flow rates, the reaction time is too short to allow for complete conversion. From our data, it is clear that a residence time of 7.5 minutes effects the highest conversion. A further increase in residence time results in a drop in yield (Fig. 3, red zone). Hence, an optimum flowrate regime was found to be situated between 0.04 to 0.06 mL min⁻¹, which corresponds to residence times of 7.5 to 5 minutes, respectively. A residence time of 7.5 minutes gave a slightly higher yield in 1-A, but was accompanied with a low amount of the corresponding sulfone 1-B (<5%). Therefore, a standard residence time of 5 minutes per run was considered optimal and, when full conversion was not achieved within a single run, the reaction mixture was reinjected to increase the overall residence time (see ESI†).

Having established insight in the governing parameters in the electrochemical oxidation of sulfides, we set out to probe the generality of our electrochemical flow protocol. Various thioethers bearing different functional groups were subjected to both Methods A and B, yielding the corresponding sulfoxide A or sulfone B, respectively (Fig. 4). For every compound, a fast potential screening was carried out to obtain the polarogram, which allows us to find the optimal condition for each compound (see ESI†). Notably, the productivity of our electrochemical flow protocol is excellent (i.e. 7.8 mmol h⁻¹ for 1-A and 5.5 mmol h⁻¹ for 1-B) providing means to scale this chemistry to quantities which are sufficient for Medicinal Chemistry applications. Further scale-up can be achieved using larger electrochemical flow reactors or via numbering-up of electrochemical microreactors.²³

As shown in Fig. 4, a wide variety of aryl, heteroaryl and alkyl thioethers were efficiently converted into their corresponding sulfoxides and sulfones in moderate to excellent yield. Functional groups, such as halides (6, 7, 11), ketones (8), esters (10, 15) and amides (9, 15), were well tolerated under our reaction conditions. Notably, nitrogen-containing heteroaromatic compounds, e.g. pyridine (12) and benzimidazole (13), can be selectively oxidized to produce the corresponding sulfoxides and sulfones without N-oxide formation. However, in the case of benzoxazole (14), nitrogen oxidation was observed at higher potentials prior to the formation of the sulfone. Interestingly, biologically relevant compounds such as the amino acid Methionine (15) and a precursor of the antiprotozoal agent Toltrazuril²⁴ (11) were efficiently oxidized in good yield. However, it is important to note that for some substrates it was not possible to access both the sulfoxide and sulfone. As an example, dibenzothiophene (5) is directly oxidized to the
sulfone. It is however plausible that a double oxidation is immediately occurring, since it is known that aromatic sulfoxides are relatively reactive. The Toltrazuril precursor (11) is oxidized only to the sulfoxide form, which can be explained by the strong electron-withdrawing character of the CF₃ group, making it less prone to oxidation. Despite the broad substrate scope, some limitations do exist to our methodology (see ESI†). Free amines, alcohols and carboxylic acids do not yield any product. In addition, thioethers bearing nitriles, aldehydes and hydroxyls at the γ-position underwent retro-Michael reactions.

Finally, the oxidation of thiols to symmetric disulfides was performed applying an analogous approach as for the oxidation of thioethers. Also here, a potential screening was carried out after which the proper voltage value was set to perform the reaction (Fig. 5). As a result, simple thiols such as thiophenol (18), benzylthiol (19) and octanethiol (20), were all converted to the corresponding disulfide in good to excellent yield. Notably, 2-mercaptopyrimidine (21) and 2-furanylmethanethiol (23) could also be converted to their disulfide derivative and were obtained in good yield. It should be noted that disulfide 23-C is prone to overoxidation under photochemical oxidation reactions, however, this was not observed using our electrochemical method. This highlights the efficiency of electrochemistry and its complementarity compared to photo-redox catalysis. Furthermore, poorly soluble starting materials like 4-mercaptobenzoic acid (22) could also be converted using this protocol.

**Conclusion**

A straightforward, green and broadly applicable electrochemical continuous-flow procedure to oxidize thioethers and thiols has been developed. Using a commercially available electrochemical flow setup (Asia Flux), a wide variety of functionalized sulfoxides (15 examples) and sulfones (15 examples) could be accessed selectively, simply by changing the applied voltage. Similarly, aryl and alkyl thiols could be efficiently oxidized to their corresponding disulfides (6 examples). Because of the sustainable nature of our developed protocol, we believe that our method is highly attractive for technical applications.
Acknowledgements

Financial support is provided by the Dutch Science Foundation (NWO) via a VIDI grant for T. N. (Grant No. 14150).

Notes and references


24 *Germany Pat*, DE3516630, 1986.

