The One-Pot Synthesis of Dihalogenated Ring-Fused Benzimidazolequinones from 3,6-Dimethoxy-2-(cycloamino)anilines using Hydrogen Peroxide and Hydrohalic Acid

Martin Sweeney,† Lee-Ann J. Keane,† Michael Gurry,† Patrick McArdle† and Fawaz Aldabbagh*†,‡

† School of Chemistry, National University of Ireland Galway, University Road, Galway, H91 TK33, Ireland
‡ Department of Pharmacy, School of Life Sciences, Pharmacy & Chemistry, Kingston University, Penrhyn Road, Kingston upon Thames, KT1 2EE, United Kingdom

ABSTRACT: 3,6-Dimethoxy-2-(cycloamino)anilines undergo 4- or 6-electron oxidations to afford novel ring-fused halogenated benzimidazoles or benzimidazolequinones using H₂O₂/HCl or H₂O₂/HBr. Cl₂ and Br₂ are capable of the same oxidative transformation to the benzimidazolequinones. Labelling experiments indicate that water is necessary for oxidation of the para-dimethoxybenzenes to the corresponding quinones.

The cleanest method of generating elemental chlorine and bromine in situ is to mix hydrogen peroxide with excess hydrochloric and hydrobromic acid respectively, since the only by-product is water (Scheme 1). The intermediate is hypohalous acid (HOX), which is commonly used to disinfect water. The molecular halogen (X₂) in water is in equilibrium with an acidic (HX) solution of HOX.3,4

Scheme 1. Generation of X₂ from H₂O₂/HX

The HOX solution has been used in the electrophilic halogenation of many aromatics.2,5-8 On the other hand, H₂O₂ in trifluoroacetic acid (TFA) has traditionally been used to give ring-fused benzimidazoles from o-cyclic amine substituted anilines.9 Recently, methanesulfonic acid (0.5-1 equiv) has replaced TFA in H₂O₂-mediated cyclizations to give alicyclic ring-fused benzimidazoles.10 In comparison, the H₂O₂/HX system is relatively underutilized in the synthesis of heterocycles with H₂O₂/HBr used to catalyze the aziridination of alkenes with chloramine T.11 One-pot H₂O₂/HX-mediated oxidative cyclization of o-cyclic amine substituted anilines with selective dichlorination and dibromination gave a series of five to eight-membered ring-fused benzimidazoles, generally in >80% yield (Scheme 2a).8

Scheme 2. H₂O₂/HX in the Preparation of Benzimidazoles and Benzimidazolequinones

Skibo and co-workers popularized aziridinyl-substituted pyrrolo[1,2-a]benzimidazolequinones as bioreductive antitumor alternatives to the mitomycins,12 and other groups reported benzimidazolequinones with useful cytotoxicity,13-21 including specificity towards hypoxic tumor cells,18 NAD(P)H:quinone oxidoreductase 1 (NQO1)19 and Fanconi anemia cells.20,21 When para-dimethoxybenzenes are precursors, a two-step HBr-mediated demethylation to the hydroquinone followed by FeCl₃-mediated oxidation is used to give the benzimidazolequinone.10,14,18,19 One-step conversion of para-dimethoxybenzenes to the desired quinones has been effected with AgO,22 Ce(NH₄)₂(NO₃)₆ (CAN),13,23-25 CoF₃,26 NBS with a catalytic amount of H₂SO₄,20,27 and PhI(OCOCF₃)₂ (PIFA).28 For one-step formation of quinones, H₂O₂/HX has advantages of high atom economy29 and low cost. The simultaneous halogenation on the aromatic or the quinone can be useful for further nucleophilic aromatic substitution14,15,30,31 and transition metal-catalyzed cross-couplings,32,33 with the resultant functionalization significantly altering biological activity.14,15,21,30,31,33 There are reports of low to moderate yields of oxidative demethylation with dihalogenation giving 5,6-dichloro- and 5,6-dibromobenzimidazolequinones using aqua regia (HNO₃/HCl (1:3))15,16 and HBr/NaBrO₃, respectively.16 However, the combination of 2-electron oxidation to the quinone with 4-electron oxidative cyclization in one-pot is unknown. Herein, we utilize H₂O₂/HX to carry out oxidative cyclization, aromatic
halogenation, and oxidative demethylation to give a new series of ring-fused dihalogenated benzimidazolequinones in mostly high yields (Scheme 2b). In all but one system, the protocol is tunable by adjusting the [H₂O₂] to [HX] ratio with high yields of the dihalogenated ring-fused dimethoxybenzimidazoles obtained when the [H₂O₂] is higher. Furthermore, the halogenation is selective to the activated aromatic or quinone moiety when an additional fused aromatic ring is in place.

Initially, 3,6-dimethoxy-2-(cycloamino)anilines 1a-1e were treated with higher amounts of H₂O₂ (10 equiv) relative to HX (5 equiv) to give, in mostly high yields and without the need for chromatography, novel ring-fused dimethoxy-substituted benzimidazoles via a 4-electron oxidative cyclization and dihalogenation (Scheme 3). 2-(Pyrolidin-1-yl)aniline 1a and 2-(piperidin-1-yl)aniline 1f were treated with higher amounts of H₂O₂ (10 equiv) relative to HX (5 equiv) to give, in mostly high yields and without the need for chromatography, novel ring-fused dimethoxy-substituted benzimidazoles via a 4-electron oxidative cyclization and dihalogenation (Scheme 3). 2-(Pyrrolidin-1-yl)aniline 1a and 2-(piperidin-1-yl)aniline 1b were found to be consumed within 20 min in MeCN under reflux to give dichlorinated and dibrominated pyrrolo[1,2-a]benzimidazoles (2a, 3a) and pyrido[1,2-a]benzimidazoles (2b, 3b) in yields of 80-92% (Scheme 3). For cyclizations of morpholine 1c, azepane 1d and azocane 1e using H₂O₂/HCl, some oxidation to the benzimidazolequinone was detected at reflux. [1,4]Oxazino[4,3-a]benzimidazole 2c, azepino[1,2-a]benzimidazole 2d, and azocino[1,2-a]benzimidazole 2e were selectively formed in good to high yields (67-95%) by lowering the reaction temperature (from reflux to 40 °C or rt) and increasing the reaction time (from 20 min to 2-24 h). Benzimidazolequinone formation was not detected in the HBr-mediated cyclizations of 1c, 1d and 1e at reflux, with 1f obtained in 89% yield, while a 6 h reaction time afforded complete dibromination to give 3d and 3e in excellent yield (92 and 95%, respectively). X-ray crystal structures for the eight-membered dichlorinated and dibrominated adducts 2e and 3e were obtained due to similarities of respective NMR spectra.

The utility of the H₂O₂/HX-mediated system was investigated using the more challenging 2-(3,4-dihydroisoquinolin-2(1H)-yl)-3,6-dimethoxyaniline (THIQ substrate) 1f with potential for halogenation on the additional aromatic ring (Scheme 3). Upon treatment of 1f (0.07 M in MeCN) with H₂O₂ (10 equiv) and HBr (5 equiv) at reflux for 20 min, oxidative cyclization was observed at the benzylic position to afford 3f in 73% yield. The isolation of dichlorinated analogue 2f proved challenging under the same conditions due to the greater reactivity of the H₂O₂/HCl system. The H₂O₂/HCl system could be tuned to deliver mono- or dichlorination. At room temperature and a 4.5 h reaction time, only monochlorination was observed, affording 4f in 60% yield, while reaction for 24 h afforded the dichlorinated product 2f in 51% yield. The site of monochlorination was confirmed by X-ray crystallography on 4f.

The room temperature reaction allowed reaction profiling by HPLC (Figure 1) with mass spectrometry detection of chlorinated aniline intermediate 1g, suggesting that chlorination of 1f occurs prior to oxidative cyclization. This observation may explain the selectivity, of other one-pot oxidative cyclizations to benzimidazoles with aromatic halogenations, which can now be assumed to be a consequence of the NH₂ of the substrate strongly directing the initial electrophilic aromatic substitution.

Scheme 3. Synthesis of Dihalogenated Benzimidazoles using H₂O₂/HX<sup>a,b</sup>

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a-1f (1.0 mmol), H₂O₂ (10 mmol), HX (5 mmol), MeCN (10 mL).</td>
<td>80%</td>
<td>2a, X = Cl, 80%</td>
<td>2b, X = Cl, 93%</td>
<td>2c, X = Cl, 95%</td>
<td>3a, X = Br, 68%</td>
<td>3b, X = Br, 92%</td>
<td>3c, X = Br, 89%</td>
</tr>
<tr>
<td>1g</td>
<td>51%</td>
<td>2f, X = Cl, 51%</td>
<td>3f, X = Cl, 51%</td>
<td>4f, X = Cl, 51%</td>
<td>5f, X = Cl, 95%</td>
<td>6f, X = Cl, 100%</td>
<td></td>
</tr>
<tr>
<td>MeCN (15 mL), 4.5 h, rt.</td>
<td>60%</td>
<td>MeCN (15 mL), 24 h, rt.</td>
<td>60%</td>
<td>MeCN (15 mL), 4.5 h, rt.</td>
<td>60%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** X-ray crystal structures showing one of the two molecules in the asymmetric unit cell for 2e and 3e with thermal ellipsoids set at 40% probability (Figures S1 & S2), and for 4f thermal ellipsoids set at 40% probability.
To carry out the one-pot overall 6-electron oxidation, to afford dihalogenated quinones, conditions which favor X₂ formation were employed (Schemes 1 and 4). H₂O₂ (50 equiv) and HCl (180 equiv) converted anilines 1a - 1d into dichlorinated ring-fused benzimidazolequinones 5a - 5d in moderate to high yields (62 - 80%) after 4 h in MeCN at 80 °C, while 5e was isolated in 54% yield. For the H₂O₂/HBr-mediated transformations, the high concentrations of HBr required for quinone formation made it desirable to perform brominations under solvent-free conditions (except for 6f, which necessitated the use of MeCN due to the lower solubility of 1f in HBr). Dibrominated analogues 6a - 6e were obtained in high yield (67 - 92%) using H₂O₂ (60 equiv) in neat HBr (30 mL) under reflux for 12 h. Ring-fused dihalogenated benzimidazolequinones (Scheme 4) were purified by flash column chromatography with the exception of dibrominated pyrrolo[1,2-a]benzimidazolequinones 6a, which was isolated cleanly without purification. X-ray crystal structures of 7,8-dichloro-3,4-dihydro-1H-[1,4]oxazino[4,3-a]benzimidazole-6,9-dione (5c), dichlorinated and dibrominated pyrrolo[1,2-a]benzimidazolequinones 5a and 6a, and azepino[1,2-a]benzimidazolequinones 5d and 6d were obtained. Isolation of significant amounts of 9,10-dichloro-5,6-dihydrobenzimidazo[2,1-a]isoquinoline-8,11-dione (5f) was however not possible by treatment of THIQ 1f with a high molar ratio of HCl relative to H₂O₂ at reflux. The reaction gave mainly inseparable products with ESI HRMS (m/z 388.9-392.9) indicative of tetrachlorination (Figure S4). This led us to employ the relatively mild conditions of H₂O₂ (10 equiv) and HCl (5 equiv) at rt, that allowed aromatic monochloride and dichloride 4f and 2f to be isolated in good yields after 4.5 and 24 h, respectively (Scheme 3, Figure 1), with extension to 72 h giving benzimidazolequinone 5f in 56% isolated yield (Scheme 4, Figure S5 for the HPLC chromatographs). The structure of 5f was confirmed by X-ray crystallography. In contrast the dibrominated analogue 6f was isolated in 68% yield from a 7 h reflux in the presence of a large excess of HBr; overbromination adducts were not detected. This is in line with the greater reactivity of Cl₂ relative to Br₂ in electrophilic halogenation reactions.34

Due to the suspected high concentration of Cl₂ or Br₂ in the one-pot 6-electron oxidative cyclizations with dihalogenation, we decided to investigate if the formation of ring-fused dihalogenated benzimidazolequinones could be effected by elemental X₂, with or without water. Chlorine gas was bubbled into a solution of anilines 1b - 1e in MeCN containing added H₂O (Table 1). Dichlorinated benzimidazolequinones 5b, 5c and 5d were isolated, but in lower yields in comparison to H₂O₂/HCl method, although 5e was given in a comparable yield of 58% in this 10 min reflux reaction. A comparative study, using 1c and Cl₂ was carried out in an equivalent amount of water (10.75 mL) to the H₂O₂/HCl protocol, however the yield of 5e was decreased further from 54% to 47%. Thus, water is required but not to the extent of the H₂O₂/HCl method. Moreover, yields deteriorated when the Cl₂ reaction was performed under anhydrous conditions with inseparable products given. Over-
chlorination of 1-methylnaphthalene was observed by Johnson et al. when Cl₂ was used under aprotic conditions. Higher yields (71-90%) were achieved for the analogous one-pot transformation giving dibrominated benzimidazolequinones 6b, 6d and 6e using Br₂ and H₂O at 40 °C for 4 h, which is indicative of the greater control achieved with less reactive Br₂ (that is not susceptible to further bromination).

Table 1. Synthesis of Dihalogenated Benzimidazolequinones using Elemental Chlorine and Bromine

<table>
<thead>
<tr>
<th>aniline</th>
<th>X</th>
<th>Y</th>
<th>n</th>
<th>yield (%)</th>
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</thead>
<tbody>
<tr>
<td>1b</td>
<td>Cl</td>
<td>CH₂</td>
<td>1</td>
<td>5b, 41</td>
</tr>
<tr>
<td>1c</td>
<td>Cl</td>
<td>O</td>
<td>1</td>
<td>5c, 54</td>
</tr>
<tr>
<td>1e</td>
<td>Cl</td>
<td>CH₂</td>
<td>2</td>
<td>5d, 71</td>
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<tr>
<td>1e</td>
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<td>CH₂</td>
<td>3</td>
<td>5e, 58</td>
</tr>
<tr>
<td>1b</td>
<td>Br</td>
<td>CH₂</td>
<td>1</td>
<td>6b, 71</td>
</tr>
<tr>
<td>1d</td>
<td>Br</td>
<td>CH₂</td>
<td>2</td>
<td>6d, 90</td>
</tr>
<tr>
<td>1e</td>
<td>Br</td>
<td>CH₂</td>
<td>3</td>
<td>6e, 90</td>
</tr>
</tbody>
</table>

*aConditions: For synthesis of dichlorides: 1 (1.0 mmol), Cl₂ (50.0 mmol), H₂O (1.8 mL), MeCN (10 mL), reflux, 10 min. For synthesis of dibromides: 1 (1.0 mmol), Br₂ (50 mmol), H₂O (1.8 mL), MeCN (10 mL), 40 °C, 4 h. *Isolated yields. *H₂O (10.75 mL).*

Finally we investigated the role of water in the quinone formation step. 7,8-Dihalo-6,9-dimethoxybenzimidazoles 2c and 3b were respectively treated with Cl₂ and Br₂ (both 50 equiv), and H₂¹⁸O (100 equiv) in MeCN (Scheme 5). The formation of the doubly ¹⁸O-labelled dihalogenated benzimidazolequinones 7c and 8b was confirmed by EI-MS (Figure S7 & S8). It follows that for both the Cl₂ and Br₂-mediated reactions, MeO-aryl bond cleavage occurred, and quinone formation did not proceed through the hydroquinone. A control experiment treating 7,8-dichloro-3,4-dihydro-1H-[1,4]oxazino[4,3-α]benzimidazole-6,9-dione 5c with H₂¹⁸O for 4 h indicated no exchange.

In conclusion, H₂O₂/HX has led to an unprecedented one-pot 6-electron oxidative transformation to yield a new series of ring-fused dihalogenated benzimidazolequinones. The elemental halogens (X₂) generated in situ from H₂O₂/HX are shown to be the active species in the oxidative synthesis. When a higher molar ratio of H₂O₂ relative to HX is employed, the X₂ concentration is lower, and the 4-electron oxidative cyclization is not accompanied by oxidation to the quinone, allowing the selective formation of a new series of ring-fused dihalogenated benzimidazoles.

ASSOCIATED CONTENT

Supporting Information (SI)
The Supporting Information is available free of charge on the ACS Publications website at DOI: XXXXXXXXXXXX.
SI contains detailed experimental, synthetic procedures, characterization data, NMR spectra and crystallographic data for all new compounds (PDF).

Accession Codes
CCDC 1863022-1863030 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting, The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author
*E-mail: f.aldabbagh@kingston.ac.uk

ORCID
Fawaz Aldabbagh: 0000-0001-8356-5258

Notes
The authors declare no competing financial interest.
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