One-Pot Hydrogen Peroxide and Hydrohalic acid Induced Ring Closure and Selective Aromatic Halogenation to give New Ring-Fused Benzimidazoles

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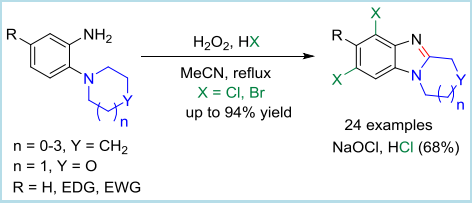
Supporting Information



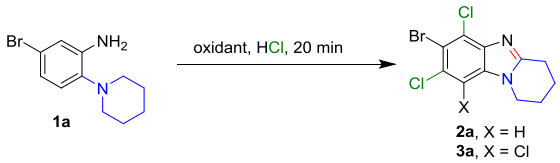
ABSTRACT: A new series of selectively dichlorinated and dibrominated five to eight-membered ring [1,2-*a*] fused benzimidazoles and [1,4]oxazino[4,3-*a*]benzimidazoles are synthesized in mostly high yields of >80% using the reaction of hydrogen peroxide and hydrohalic acid with commercially available *o*-cyclic amine substituted anilines. Domestic bleach with HCl is also capable of a one-pot ring-closure and chlorination.

The combination of hydrogen peroxide and hydrohalic acid (HX, where X = Cl, Br) is a source of electrophilic chlorine and bromine that can be used for facile aromatic halogenations.[1-4] Moreover H_2O_2 and HCl has been reported to give 4,6-dichlorination of 5-hydroxybenzimidazole.[5] 1-Chlorobenzimidazole can be formed by reacting benzimidazole with sodium hypochlorite (NaOCl) in CCl_4.[6] The intermediate of the reaction between H_2O_2 and HCl is hypochlorous acid (HOCl), which is commonly used to disinfect water, and its salt is the active ingredient in domestic bleaches. The oxidizing solution is very cheap, low in molecular weight, and allows the *in situ* generation of elemental chlorine and bromine with the by-product being water. Therefore there are significant green and technical advantages to using H_2O_2-HX in organic synthesis.

More than fifty years ago, it was recognized that a combination of H_2O_2 and trifluoroacetic acid could be used to prepare ring-fused benzimidazoles in good yields from *o*-cyclic amine substituted anilines.[7] The use of o-*tert*-aminoacetanilides with peroxide (including H_2O_2[8] and Oxone[9]) in formic acid is recognized as a versatile method for preparing ring-fused benzimidazoles and imidazobenzimidazoles. The preparation of 2-aryl substituted benzimidazoles was reported from the condensation of aryl aldehydes with *o*-phenylenediamines in the presence of H_2O_2-HCl.[10] Moderate yields of benzimidazoles and ring-fused benzimidazoles with tetrachlorination of the fused benzene part was reported using the reaction of sulfuryl chloride with *o*-aminodialkylanilines.[11]

Halogenated benzimidazoles have anti-cancer,[12, 13] anti-protozoal,[13] anti-tuberculosis,[14] and anti-hepatitis activity,[15] as well as, dopamine-receptor binding.[16] In addition to their biological activity, benzimidazoles chlorinated and brominated at specific sites provide promise as valuable synthetic intermediates. Halogenations of heterocycles are generally carried out in subsequent synthetic step(s) and require the use of difficult to handle Cl_2, Br_2 or organic reagents prepared from them. The halogenation of the heterocycle is often associated with low selectivity and when organic reagents are used waste by-products are generated. Our objective was thus to accomplish a one-pot reaction that combined the aromatic halogenation capacity of H_2O_2-HX with the oxidative cyclization of *o*-cyclic amine substituted anilines to form a new series of valuable halogenated ring-fused benzimidazoles. Herein, is reported the first preparation of specifically dichlorinated and dibrominated ring-fused benzimidazoles from commercially available anilines.

Table 1. Optimization of Reaction Conditions



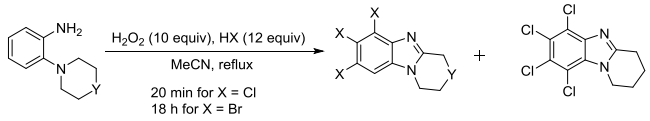
entry	oxidant	solvent	temp	yield of **2a** (%)
1	H_2O_2	MeCN	rt	trace
2	H_2O_2	MeCN	rt[a]	73
3	H_2O_2	MeCN	50 °C	81
4	H_2O_2	MeCN	reflux	**90**
5	H_2O_2	THF	reflux	83
6	H_2O_2	MeOH	reflux	50[b]
7	NaOCl	MeCN	reflux	68[c]
8	household bleach[d]	MeCN	reflux[e]	56

Conditions: Aniline **1a** (1.0 mmol), oxidant (10 mmol), HCl (12 mmol), solvent (10 mL); [a]4 h; [b]recovery of **1a** (38%); [c]Plus **3a** in 15% yield; [d]20 mL of Parazone® thin bleach; [e]1 h

Initially we attempted to establish the one-pot oxidative cyclization and chlorination on 5-bromo-2-piperidin-1-ylaniline **1a** in acetonitrile (Table 1). Excess molar amounts of concentrated HCl relative to H_2O_2 were found necessary, and the reaction times were reduced on heating. Monitoring of the reaction by TLC showed the total consumption of aniline **1a** within 20 minutes using the optimized conditions (entry 4). 6,8-Dichloroinated pyrido[1,2-*a*]benzimidazole **2a** was isolated in 90% yield after basic work-up without the requirement for chromatography. This transformation was found to also work in THF and methanol, however yields of **2a** were reduced, and a cleaner reaction occurred in acetonitrile. The sodium salt of hypochlorous acid formed *in situ* is commonly used in domestic bleaches. We thus decided to replace

H_2O_2 with NaOCl solution, and found that the desired **2a** could be isolated in 68% yield, although chromatography was required to separate some trichlorinated benzimidazole **3a** formed in 15% yield. The reaction was then carried out using a well-known brand of household bleach (containing an unspecified quantity of NaOCl) to exclusively give 6,8-dichloro adduct **2a** in 56% yield with the reduced yield attributed to the purification by chromatography, which separated a number of additives (presumably surfactants and perfumes) in the bleach.

Scheme 1. One-Pot Ring-Fused Benzimidazole Formation with Aromatic Trihalogenation



1b, Y = CH_2
1c, Y = O

2b, X = Cl (71%)
2c, X = Cl (89%)
4c, X = Br (87%)

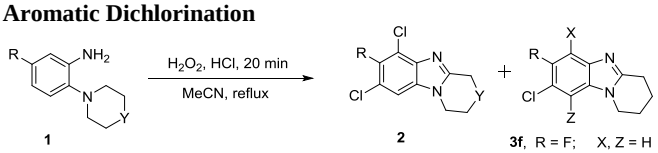
3b (12%)

Using the optimized conditions (Table 1, entry 4) the scope and versatility was explored. Firstly we attempted to investigate *o*-cyclic amine substituted anilines devoid of other aromatic substituents (Scheme 1). 2-Piperdin-1-ylaniline **(1b)** and 2-morpholin-4-ylaniline **(1c)** gave the respective trichlorinated ring-fused benzimidazoles **2b** and **2c** in 71 and 89% yield. Tetrachlorination product **3b** in 12% yield was separated by column chromatography from **2b**. Replacing HCl by concentrated HBr transformed piperidine **1b** into dibrominated pyrido[1,2-*a*]benzimidazole **4b** in 94% yield (Table 3), although under the same conditions the morpholine analogue was tribrominated to give **4c** in 87% yield (Scheme 1). Attempts at isolating dibrominated benzimidazole from the reaction of **1c** at shorter reaction times were unsuccessful due to the isolation of mixtures of brominated benzimidazoles, and a clean transformation occurred by increasing the reaction time to 18 hours to give exclusively **4c**.

The preparation of selectively dichlorinated ring-fused benzimidazoles from various *o*-cyclic amine substituted anilines containing electron-donating and electron-withdrawing groups proved mostly facile with yields of 72-92% obtained of ring-fused benzimidazoles (Table 2). The substitution of the chlorine atoms was consistent, and did not vary with the nature of the substituent on the aniline, as confirmed by X-ray crystal structures of adducts **2d** and **2i** (Figure 1).[17] In some cases chromatography was required to separate small amounts of fully chlorinated benzimidazoles **3b** and **3h**, although 5-fluoro-2-piperidin-1-ylaniline **(1f)** tended to prefer cyclization with monochlorination to give **3f** in 62% yield with the dichlorinated adduct **2f** given in smaller yield of 27%.

Beginning with the optimized conditions (Table 1, entry 4) and replacing HCl with HBr, the preparation of dibrominated ring-fused benzimidazoles was investigated (Table 3). In some cases the latter reaction conditions used successfully to yield dichlorinated ring-fused benzimidazoles (Table 2) did not require modification, although significantly longer reaction times were required for resonance activators (NHAc and OMe) on the aniline.

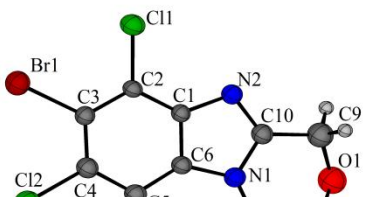
Table 2. One-Pot Ring-Fused Benzimidazole Formation with Aromatic Dichlorination



1 **2** **3f**, R = F; X, Z = H
3h, R = CN; X, Z = Cl

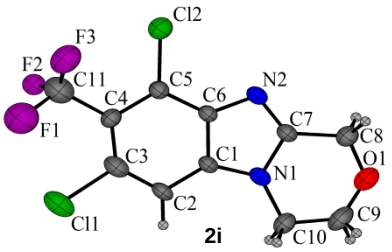
Conditions: Same as in Table 1, entry 4

Figure 1. Crystal Structures of 7,9-dichloro-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]benzimidazoles



1	R	Y	yield (%)
1a	Br	CH_2	**2a**, 90
1d	Br	O	**2d**, 92
1e	Cl	CH_2	**2b**, 73 + **3b**, 15
1f	F	CH_2	**2f**, 27 + **3f**, 62
1g	Me	CH_2	**2g**, 82
1h	CN	CH_2	**2h**, 79 + **3h**, 12
1i	CF_3	O	**2i**, 72
1j	NHAc	CH_2	**2j**, 88
1k	OMe	O	**2k**, 87

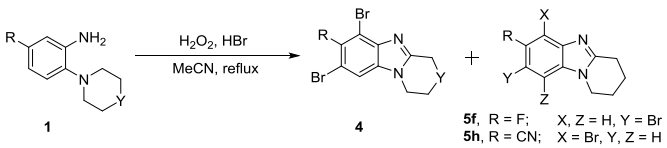
2d



2i

Nevertheless dibrominated ring-fused benzimidazoles were isolated in excellent yield of 74-94% and without the requirement for chromatography, save for three anilines containing electron-withdrawing groups (F, CN, CF_3). The substitution pattern was the same as for the chlorination, and the positions for the bromination did not vary with the nature of the substituent on the aniline, as confirmed by X-ray crystal structures of dibrominated adducts **4b**, **4f** and **4m** (Figure 2).[17] Analogous to the results obtained with H_2O_2-HCl, 5-fluoro-2-piperidin-1-ylaniline **(1f)** gave significant monobromination at pyrido[1,2-*a*]benzimidazole C-8 with **5f** separated in 31% yield from the desired dibrominated adduct **4f** isolated in 56% yield. Surprisingly, the benzonitrile **1h**, which gave some polychlorination with H_2O_2-HCl after only 20 minutes, was found difficult to dibrominate with only the monobromide **5h** isolated in 62% yield. Further, no brominated benzimidazoles could be cleanly separated from the attempted reaction with 5-(trifluoromethyl)aniline **1i**, although the same substrate gave selectively 7,9-dichlorinated [1,4]oxazino[4,3-*a*]benzimidazole **2i** in 72% yield using H_2O_2-HCl (Table 2). Thus, it seems that the bromination is more strongly affected by substituents on the aniline than the chlorination with electron-withdrawing substituents making dibromination difficult.

Table 3. One-Pot Ring-Fused Benzimidazole Formation with Aromatic Dibromination



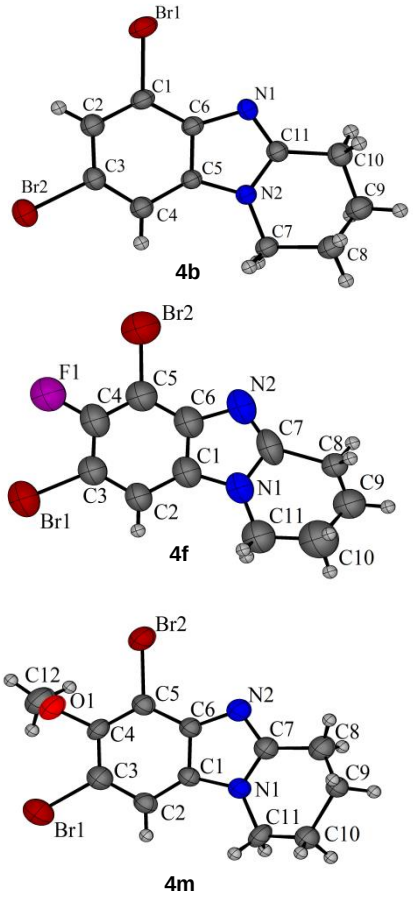
1 **4**

5f, R = F; X, Z = H, Y = Br
5h, R = CN; X = Br, Y, Z = H

1	R	Y	time	yield (%)
1a	Br	CH_2	20 min	**4a**, 89
1b	H	CH_2	20 min	**4b**, 94
1d	Br	O	20 min	**4c**, 92
1e	Cl	CH_2	40 min	**4e**, 93
1f	F	CH_2	20 min	**4f**, 56[a] + **5f**, 31[a]
1g	Me	CH_2	20 min	**4g**, 84
1h	CN	CH_2	20 min	**5h**, 62[a,b]
1i	CF_3	O	20 min	**4i**, 0[a,c]
1j	NHAc	CH_2	2 d	**4j**, 74[d]
1k	OMe	O	8 h	**4k**, 92

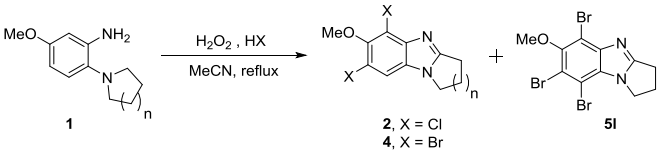
Conditions: Aniline **1** (1.0 mmol), H_2O_2 (10 mmol), HBr (12 mmol) in MeCN (10 mL); [a]Additional times and equivalents produced similar results; [b]**4h** observed but was not isolated; [c]Intractable mixture of mono and non-brominated ring-fused benzimidazole; [d]H_2O_2 (20 mmol), HBr (24 mmol) in MeCN (10 mL).

Figure 2. Crystal Structures of 6,8-dibromo-1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazoles



The synthesis of alternative [1,2-*a*] alicyclic ring-fused benzimidazoles was examined (Table 4). Selectively dichlorinated five to eight-membered [1,2-*a*] alicyclic ring fused benzimidazoles **2l-2o** were isolated in 78-93% yield after reaction times of 20 minutes. The brominations were found to be significantly slower than the analogous chlorinations, and double the number of equivalent of H_2O_2-HBr were required to obtain the desired products. This is in agreement with literature kinetic studies for the halogenation of *p*-xylene, where Br_2 was found to react more than 200 times slower than Cl_2.[18] Attempts were made to reduce reaction times by activating bromine towards electrophilic attack by adding a quaternary ammonium salt (TBAB),[2] but no effect on rate was observed. Our system is however different to the literature,[2] as there is an absence of a two-phase system due to the solubility of acetonitrile in water. It is conceivable that steric factors might be also influencing the rate of electrophilic aromatic bromination, since one would have expected greater polarizability in suspected bromination species, H_2O^+-Br and Br_2 compared to the chlorine analogues.[3] Nevertheless selectively dibrominated pyrido-, azepino- and azocino [1,2-*a*] ring-fused benzimidazoles **4m-4o** were isolated in high yields of 70-86%. Monitoring the reaction of **1l** with H_2O_2-HBr using ^{1}H NMR showed after 20 minutes the formation of a mixture of monobromides; 5- and 7-bromobenzimidazoles in an approximate 1:3 ratio and after 20 hours a mixture of di- and tribromides **4l** and **5l** remained in an approximate 2:1 ratio. It was thus not possible to cleanly isolate 5,7-dibromopyrrolo[1,2-*a*]benzimidazole **4l**, and it was decided to allow the tribromide **5l** to be regioselectively formed in 87% yield.

Table 4. One-Pot Five to Eight-Membered [1,2-*a*] Ring-Fused Benzimidazole Formation with Aromatic Dihalogenation



1	X	n	time	yield (%)
1l	Cl	1	20 min	**2l**, 93
1m	Cl	2	20 min	**2m**, 90
1n	Cl	3	20 min	**2n**, 89
1o	Cl	4	20 min	**2o**, 78
1l	Br	1	4 d	**5l**, 87
1m	Br	2	4 d	**4m**, 86
1n	Br	3	5 d	**4n**, 80
1o	Br	4	5 d	**4o**, 70

Conditions: Aniline **1** (1.0 mmol) in MeCN (10 mL) with H_2O_2 (10 mmol) and HCl (12 mmol) for X = Cl or with H_2O_2 (20 mmol) and HBr (24 mmol) for X = Br.

In conclusion we have successfully established a simple and inexpensive H_2O_2-HX preparation of halogenated ring-fused benzimidazoles with 31 new compounds now reported from commercial anilines. In most cases the one-pot transformation gives regioselectively the novel dihalogenated heterocycle in high yields.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for all compounds, including X-ray crystallographic data for compounds **2d**, **2i**, **4b**, **4f** and **4m** is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The Authors declare no competing financial interest.

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17. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 1054365 for (**2d**) CCDC 1054369 for (**2i**), CCDC 1054366 for (**4b**), CCDC 1054368 for (**4f**), and CCDC 1054367 for (**4m**).
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