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Green halogenation of aromatic heterocycles using ammonium halide and hydrogen peroxide in acetic acid solvent

Danielle N. D'Aleo, Sheena R. Allard, Cassandra C. Foglia, Shawna L.M. Parent, David J. Rohr, Christine Gottardo, and Craig D. MacKinnon

Abstract: The green generation of X^+ (X = Br, I) using hydrogen peroxide in aqueous acetic acid allows access to aromatic heterocyclic halides in yields and purities comparable to syntheses employing *N*-bromosuccinimide. In activated and unsubstituted thiophene rings, regioselectivity is quantitative for positions α to the sulfur; pyrroles also give quantitative reactions, at least initially. Deactivated rings, including furans and thiazoles, as well as thiophenes with strongly electron-withdrawing groups showed little to no reactivity under the conditions investigated. The reaction shows remarkable functional group tolerance (to alcohol, nitro, alkyl, halo, and carbonyl groups), as shown through reaction with substituted phenols. In all bromination reactions, reaction yields and regiochemistry were very similar to reactions involving *N*-bromosuccinimide in tetrahydrofuran solvent.

Key words: bromination, iodination, thiophenes, green chemistry, heterocyclic chemistry.

Résumé : La production verte de X^+ (X = Br, I) au moyen de peroxyde d'hydrogène dans une solution aqueuse d'acide acétique donne accès aux halogénures hétérocycliques aromatiques avec des rendements et des puretés comparables à ceux des synthèses en utilisant le *N*-bromosuccinimide. Dans les noyaux thiophènes activés et non substitués, la régiosélectivité est quantitative pour les positions en α du soufre; les pyrroles donnent aussi des réactions quantitatives, du moins initialement. Les noyaux désactivés, y compris les furanes et les thiazoles, ainsi que les thiophènes porteurs de groupes fortement électroattracteurs ne manifestent que peu de réactivité, voire aucune, dans les conditions étudiées. La réaction présente une tolérance remarquable aux groupements fonctionnels (groupes alcool, nitro, alkyle, halo et carbonyle), comme le montre la réaction avec des phénols substitués. Dans toutes les réactions de bromation, le rendement et la régiosélectivité étaient très semblables à ceux des réactions faisant appel au *N*-bromosuccinimide en solution dans le tétrahydrofurane. [Traduit par la Rédaction]

Mots-clés : bromation, iodation, thiophènes, chimie verte, chimie hétérocyclique.

Introduction

The tenets of green chemistry[1] include the use of nontoxic solvents and atom economy, and pursuing green alternatives to common reactions is an area of current interest. One such focus is synthetic routes to organic halides, as the halide functionality is common in many C–C bond-formation reactions (e.g., via the Suzuki,[2] Stille,[3] and Sonogashira[4] methods); this topic has been recently reviewed.[5] Green halogenations of phenyl rings are available, provided the ring is activated and (or) if a metal-based catalyst is used. The key step is the creation of "Cl^+", "Br^+", or "I^+" using a nontoxic oxidant. Oxidizing the elemental halogen X_2 gives the greatest atom economy, but X_2 must have been previously generated from a naturally occurring halide salt that in the case of bromine is a toxic and corrosive liquid and in the case of Cl_2 is a toxic and corrosive gas. Thus, ways to generate "X^+" in situ are preferable. Brominations and iodinations are more important targets because their compounds are much more commonly used in coupling reactions than chlorinated organics.

Green halogenations of aromatic heterocycles have not been systematically investigated, except in the case of the pyrazole ring.[6] Our interest in substituted oligothiophenes[7–9] as molecular semiconductors[10,11] led us to search for a green route to bromo- and iodothiophenes for use in subsequent C–C coupling reactions. Our substrate and its end-use as a semiconductor material suggested some initial design requirements: the oxidant cannot oxidize the thiophene sulfur to the *S*,*S*-dioxide and it should be metal-free. Previous synthetic generations of "X^+" have tended to use a metal-based catalyst,[12–14] but elimination of even trace amounts of metals is vitally important in semiconductors, where incidental doping will damage device performance. Similarly, the pharmaceutical industry would prefer metal-free reactions when possible to avoid accumulation of toxic metals in long-term medication regimens.

One metal-free generation of "Br^+" uses nitric acid,[15] which is too oxidizing for thiophenes.[16] Another uses Br_2/HBr, but multibromination occurs.[17] The remaining oxidants that met our requirements were hydrogen peroxide[18,19] and oxone.[20] The latter contains a mixture of potassium salts, so we chose the peroxide as having a smaller environmental footprint and better atom economy. The "Br^+" is generated by mixing hydrogen peroxide in glacial acetic acid with the ammonium halide, which gives CH_3CO_2X (Scheme 1).

Herein, we show that this reaction will generate the same products, in comparable yield, as the reaction of *N*-bromosuccinimide (NBS) in tetrahydrofuran solvent. The heterocyclic substrates tested contain a thiophene, furan, thiazole, or pyrrole ring. We also include the reactions of several substituted phenols to test the functional group tolerance of the reaction conditions.

Results and discussion

The full results are reported in Tables 1 and 2 (Scheme 2 gives the abbreviation codes). Reactions were followed by GC using a

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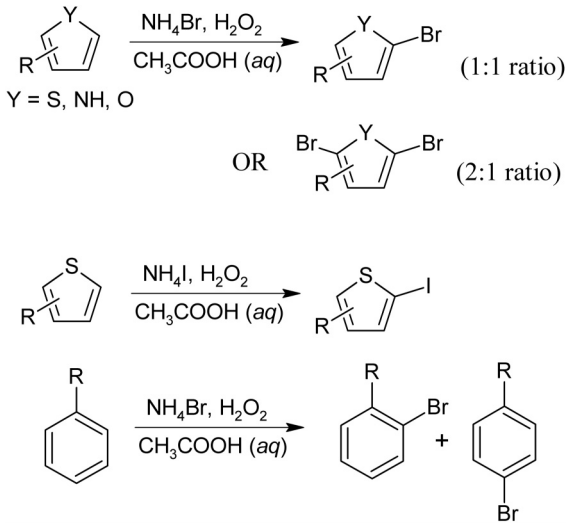
D.N. D'Aleo, S.R. Allard, C.C. Foglia, S.L.M. Parent, D.J. Rohr, C. Gottardo, and C.D. MacKinnon. Department of Chemistry, Lakehead University, 955 Oliver Road, Thunder Bay, ON P7B 5E1, Canada.

Corresponding author: Craig D. MacKinnon (e-mail: craig.mackinnon@lakeheadu.ca).

Scheme 1. Green halogenation reactions of this study.



flame ionization detector for quantitation. Yields were calculated as relative amounts compared with the total area under the GC peaks. When necessary, the reaction mixture was spiked with a known amount of nitrobenzene (which does not halogenate under these conditions) to ensure that all of the substrate is accounted for in the product GC. When possible, we also cross-checked the GC ratios with ^{1}H NMR integration ratios by isolating the product mixtures. Peroxide was found to be an appropriate oxidant, as there is no evidence for *S*,*S*-dioxides in any of the thiophene reactions, nor was there any reaction with the ammonium from the bromide and iodide salts. The regiochemistry of the products was determined by comparison of GC retention times with those of the commercially available halogenated product(s). When unavailable, presumed products were synthesized by literature methods and GC times compared, or the products were identified by a combination of NMR and GC–MS. Reactions were allowed to run for a maximum of 20 h under ambient conditions; as a corollary to our desire to utilize a green reaction, we wanted a simple methodology, using minimal equipment and time.

For comparison, brominations using NBS in tetrahydrofuran were performed (in the dark) over the same length of time as the "Br^+" brominations. Selected results are given in Tables 1 and 2; the full results are included in the supplemental material. They show that the regioselectivity of the green reaction is similar to that of the NBS reaction. In one case (compare entries 2 and 6), the green halogenation method significantly outperforms the NBS method in selectivity, if not in time.

Functional group tolerance was tested on a number of substituted thiophenes; to increase the variety of functional groups, we also used aniline and a number of substituted phenols,[21] as the latter are more readily available and cheaper than the equivalent thiophenes. As shown in Tables 1 (thiophenes) and 2 (benzenes), the peroxide does not react with any of the electron-donating functional groups tested, nor with halogens (with the exception of entry 14). Substrates with electron-withdrawing groups (benzaldehyde, cyanobenzene, nitrobenzene, and chlorobenzene) also showed functional group tolerance, but unfortunately, in concordance with what was previously observed for other phenyl substrates,[18,19] the electron-withdrawing groups deactivated their rings to substitution. Thus, several substrates did not react with "Br^+" or "I^+" to any significant extent, defined herein as having greater than 90% starting material remaining after 20 h with a 1:1 stoichiometry. They are as follows (percentage of starting material remaining in parenthesis): 3-methylthiophene-2-carbonitrile (100), 1,3-thiazole (100), imidazole (100), benzofuran (91), chlorobenzene (100), benzonitrile (100), and nitrobenzene (100). The lack of reactivity of thiazole and imidazole is likely due to the acidic conditions of the reaction, which caused protonation of the pyridine-like nitrogen (to create =NH^+–), thereby deactivating the ring to electrophilic aromatic substitution. Akin to the previously observed reactivity of *p*-nitroaniline,[18,22] the donor–acceptor compound *p*-nitrophenol did react (entries 31 and 32), but the sulfur in the thiophene ring is apparently not sufficiently activating in 3-methylthiophene-2-carbonitrile or 3-methylthiophene-2-carboxaldehyde.

There are also cases where bromination will occur, while iodination will not, i.e., brominated thiophenes will react with "Br^+" but not with "I^+". As such, 2-bromo-5-iodothiophene **1-BrI** is not accessible by iodinating bromothiophene, but is accessible through bromination of iodothiophene (entry 13) if the stoichiometry is strictly kept at 1:1. Otherwise, some dibromothiophene **1-Br$_2$** is created (entry 14).

Although peroxide is sufficient to oxidize chloride from HCl in petroleum ether solvent,[23] we saw no evidence of chlorination using an ammonium chloride – hydrogen peroxide mix under our conditions. Furan did not react cleanly and benzofuran was mostly starting material even after 24 h of reaction time. The in situ GC results appear promising for pyrrole (entries 23–26), but the regiochemical location of the halogen could not be determined. Attempts at isolating the product(s) consistently gave an intractable black material, presumably a form of polypyrrole, which is unsurprising given that the first synthesis of polypyrrole involved an oxidative coupling using hydrogen peroxide.[24,25]

Both phenol (entries 27 and 28) and aniline (entries 33 and 34) undergo *o*- and *p*-substitution (Table 2), indicating that the reactive species is the neutral phenol and aniline. There is no evidence of *m*-substitution, even though the acidic conditions should create a significant fraction of protonated molecules, which would be *m*-directing. We conclude that the deactivating nature of the –NH^+_3 and –OH^+_2 groups prevents reaction with any molecules on the protonated side of the equilibrium, thereby preventing *m*-substitution from occurring. These results are consistent with those previously published.[18]

This reaction can be considered green because of the relative environmental benignity of the solvent, reactants, and byproducts. There are several metrics used to measure greeness. One of the most common is Sheldon's *E*-factor, but it neglects to take into account the nature of the materials and solvents,[26] which is the parameter we are improving upon. A more useful metric for our purposes is the EcoScale,[27] which applies "penalty points" to toxic or flammable materials, inefficient steps in a synthesis, etc. Table 3 shows the EcoScale calculation, which gives a result of 2–16 penalty points in favour of our green reaction over a typical NBS reaction.

For the GC reactions, we used a standard organic/aqueous separation workup primarily to ensure that salts, etc., did not clog up the GC column; such a workup would not normally be considered "green". To show that this extraction step would not be necessary in preparatory-scale reactions, we performed two reactions (**1-Br** → **1-Br$_2$** and **4** → **4-Br$_2$**) on a preparatory scale with a green workup. The procedure involved removal of the acetic acid by rotary evaporation followed by addition of water to dissolve the product salts and unreacted starting materials. For **1-Br$_2$**, the product is an insoluble oil, which was isolated using a Pasteur pipette. The nonoptimized yield was only 36%. However, when isolating the solid product **4-Br$_2$** by filtration, the yield is considerably better at 76%. In both cases, the purity is very high (no evidence of any impurities, starting materials, or side-products in the ^{1}H NMR; see Figs. S1 and S2 in the supplementary information), indicating the potential for a truly green isolation process once conditions are optimized.

Table 1. Results for bromination and iodination reactions using heterocyclic substrates.

				Species in final reaction mixture (relative ratios by GC)					
Entry	Substrate	Halide source, molar ratio	Time (h)	Unreacted substrate	1:1 product	2:1 product	Other products[a]	Notes	Identification method[b]
1[c]	**1**	Br^+, 1 equiv.	20	12%	80% **1-Br**	8% **1-Br$_2$**			GC
2[c]	**1**	Br^+, 2 equiv.	20			99% **1-Br$_2$**			GC
3	**1**	I^+, 1 equiv.	20	23%	76% **1-I**	trace **1-I$_2$**			GC
4	**1**	I^+, 2 equiv.	20	24%	76% **1-I**	trace **1-I$_2$**			GC
5	**1**	NBS[d], 1 equiv.	4	3%	79% **1-Br**	18% **1-Br$_2$**		No change after 4 h	GC
6	**1**	NBS[d], 2 equiv.	4		59% **1-Br**	41% **1-Br$_2$**		No change after 4 h	GC
7	**2**	Br^+, 1 equiv.	20		93% **2-Br**	7% **2-Br$_2$**			NMR/MS
8	**2**	Br^+, 2 equiv.	20		Trace **2-Br**	99% **2-Br$_2$**			NMR/MS
9	**2**	I^+, 1 equiv.	20	1%	98% **2-I**	1% **2-I$_2$**			NMR/MS
10	**2**	I^+, 2 equiv.	20		90% **2-I**	10% **2-I$_2$**			NMR/MS
11	**3**	Br^+, 1 equiv.	20	14%	86% **3-Br**				NMR/MS
12	**3**	Br^+, 2 equiv.	20		93% **3-Br**	7% **3-Br$_2$**[e]			NMR/MS
13	**1-I**	Br^+, 1 equiv.	20		99% **1-BrI**				NMR/MS
14	**1-I**	Br^+, 2 equiv.	20		57% **1-BrI**		40% **1-Br$_2$**		NMR/MS,GC
15[c]	**4**	Br^+, 1 equiv.	20	7%	63% **4-Br**	31% **4-Br$_2$**			GC
16[c]	**4**	Br^+, 2 equiv.	20			99% **4-Br$_2$**			GC
17	**4**	I^+, 1 equiv.	20	9%	72% **4-I**	18% **4-I$_2$**			NMR/MS
18	**4**	I^+, 2 equiv.	20		9% **4-I**	91% **4-I$_2$**			NMR/MS
19	**5**	Br^+, 1 equiv.	20	52%	48% **5-Br**				NMR/MS
20	**5**	Br^+, 2 equiv.	20		99% **5-Br**				NMR/MS
21	**5**	NBS[d], 1 equiv.	20	27%	73% **5-Br**				NMR/MS
22	**5**	NBS[d], 2 equiv.	20		99% **5-Br**				NMR/MS
23	**6**	Br^+, 1 equiv.	20		69% **6-Br**[e]	29% **6-Br$_2$**[e]		Could not isolate	MS
24	**6**	Br^+, 2 equiv.	4		99% **6-Br**[e]			Decomposes within 20 h	MS
25	**7**	Br^+, 1 equiv.	20	Trace	99% **7-Br**[e]			Could not isolate	MS
26	**7**	Br^+, 2 equiv.	4	Trace	99% **7-Br**[e]			Decomposes within 20 h	MS

[a]Because the substrates are reagent grade, trace byproducts appear in the gas chromatogram.
[b]GC, product identified using retention times of known materials; NMR, product identified by NMR; MS, product identified by GC–MS.
[c]Quantified using a nitrobenzene spike.
[d]Representative examples of NBS bromination for comparison with the "Br^+" method; a complete table containing all NBS reactions is given in the supplementary material.
[e]Regiochemistry of substitution could not be definitively determined.

Table 2. Results for phenol (and aniline) substituents.

				Species in final reaction mixture (relative ratios by GC)				
Entry	Substrate	Halide source, molar ratio	Time (h)	Unreacted substrate	1:1 product	2:1 product	Other products[a]	Identification method[b]
27	Phenol	Br^+, 1 equiv.	20	14%	38% *o*-bromo 39% *p*-bromo	9% 2,4-dibromo		NMR/MS,GC
28	Phenol	Br^+, 2 equiv.	20		0% *o*-bromo 10% *p*-bromo	82% 2,4-dibromo	8% Tribromo[c]	NMR/MS,GC
29	2-Naphthol	Br^+, 1 equiv.	20	Trace	99% 1-bromo		Trace	NMR/MS
30	2-Naphthol	Br^+, 2 equiv.	20		99% 1-bromo		Trace	NMR/MS
31	4-Nitrophenol	Br^+, 1 equiv.	20	31%	36% 2-bromo	33% 2,6-dibromo		NMR/MS
32	4-Nitrophenol	Br^+, 2 equiv.	20			95% 2,6-dibromo	Multiple trace	NMR/MS
33	Aniline	Br^+, 1 equiv.	20	10%	16% *o*-bromo 57% *p*-bromo	16% 2,4-dibromo		GC[d]
34	Aniline	Br^+, 2 equiv.	20			91% 2,4-dibromo	9% tribromo[c]	GC[d]

[a]Because the substrates are generally reagent grade, there are often trace byproducts in the gas chromatogram.
[b]GC, product identified using retention times of known materials; NMR, product identified by NMR; MS, product identified by GC–MS.
[c]GC–MS shows a tribromo species, but no attempt was made to separate this product to definitively characterize it.
[d]GC peaks assigned by analogy with reference 17; the identities were confirmed by NMR and MS analysis.

Conclusions

In conclusion, we have demonstrated an efficient green halogenation reaction for electron-rich heterocyclic rings. The conditions lead to highly selective substitutions on sites α to the heteroatom. Dibromination of both α positions, or monobromination when the second α position already contains a functional group, proceed quantitatively. As expected,[18,22] the results in Table 2 show that regioselectivity for phenols was not as good as for thiophenes, with significant amounts of both *o*- and *p*-substitution. Reactions are comparable in selectivity and yields to typical NBS substitutions. Given that the effectiveness of the two methods is similar, the "X^+" method is greener, with the significant advantages of environmentally benign waste products and solvent.

Experimental section

Materials

The following materials were synthesized by literature methods: **4**,[28] **4-Br**,[29] and **4-Br$_2$**[29]; 3-methylthiophene-2-carbonitrile

Scheme 2. Substrates and products in this study.

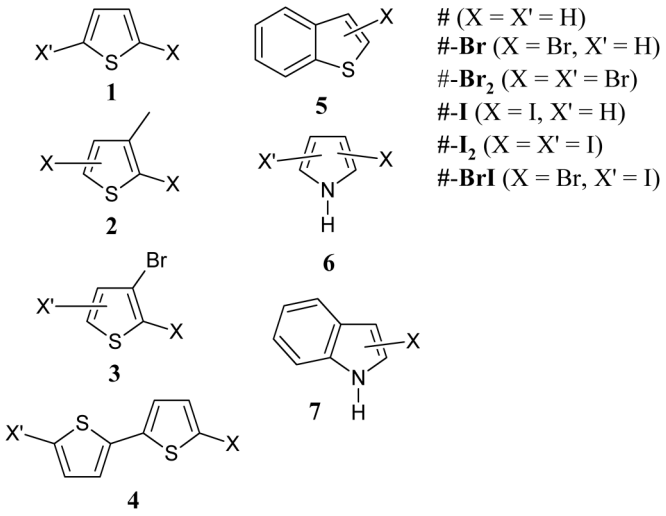


Table 3. Calculation of EcoScale penalty points.

Parameter	NBS	"X+"	Notes
1. Yield	na	na	Yields similar by GC
2. Price of reaction components	0	0	All components <$10/mmol product
3. Safety			
Toxic byproduct	5	0	Succinimide vs. ammonium acetate
Toxic solvent	5	0	Tetrahydrofuran vs. acetic acid
Flammable solvent	5	0	Tetrahydrofuran vs. acetic acid
4. Technical setup	0	1	"X+" reaction requires dropwise addition of H_2O_2
5. Temperature/time	1	1	Room temperature reaction, 1 h < reaction time < 24 h
6. Workup/purification	0	0	Both solvents have boiling point temperature <150 °C, everything else will be the same
Total	16	2	

was synthesized by the method given below. All other materials were obtained commercially (>95% purity) and used as received.

General procedure for green halogenation reactions

Substrate (2.0 mmol) and ammonium halide (NH_4Br or NH_4I, 2.2 mmol for monohalogenation, 4.4 mmol for dihalogenation) were stirred in glacial acetic acid (4 mL) for 5 min, after which 30% hydrogen peroxide solution (0.23 mL for monohalogenation, 0.46 mL for dihalogenation) was added dropwise. The mixture was stirred for the time given in Tables 1 and 2 (4–20 h), then the mixture quenched with sodium bicarbonate solution and extracted into CH_2Cl_2. This organic layer was injected into the GC–FID to give the relative yields summarized in the tables or rotary evaporated to isolate the product for NMR analysis. GC–FID yields are the area under a given peak as a percentage of the sum of peak areas for all peaks. They are uncorrected for differences in detector response for different species except where noted.

Isolation-scale synthesis of 2,5-dibromothiophene (1-Br$_2$)

In acetic acid (60 mL), 2-bromothiophene (4.90 g, 30 mmol) and ammonium bromide (3.23 g, 33 mmol) were dissolved followed by dropwise addition of 4.48 mL (40 mmol) of 30% hydrogen peroxide. The mixture was stirred overnight (16 h). The acetic acid was removed using a rotary evaporator and then 20 mL of water added to dissolve the residual ammonium salts and peroxide. The product separated as a pale yellow oil, removed using a Pasteur pipette (2.66 g, 36%). ^{1}H NMR is identical to commercially available material; no evidence of impurities present.

Isolation-scale synthesis of 5,5′-dibromo-2,2′-bithiophene (4-Br$_2$)

In acetic acid (4.0 mL), bithiophene (0.32 g, 1.9 mmol) and ammonium bromide (0.43 g, 4.4 mmol) were dissolved followed by dropwise addition of 0.23 mL (2 mmol) of 30% hydrogen peroxide. The mixture was stirred overnight (16 h). The acetic acid was removed using a rotary evaporator and then 10 mL of water added to dissolve the residual ammonium salts and peroxide. The solid product was filtered to give 0.76 g of product (76%). ^{1}H NMR is identical to material synthesized by the literature route;[29] no evidence of starting materials, monobrominated product **4-Br**, or other impurities present.

Synthesis of 3-methylthiophene-2-carbonitrile

Although commercially available, we synthesized this compound as follows. The acid chloride of 3-methylthiophene-2-carboxylic acid was generated by refluxing the acid (2.01 g, 14.2 mmol) in $SOCl_2$ (6 mL) for 10 min. The residual $SOCl_2$ was removed in vacuo and the chloride converted to the amide upon addition of aqueous ammonium hydroxide (15 mL) and warming (to 75 °C) for 30 min. The resultant solid was suction filtered, washed copiously with water, and dried. Without further purification, 0.51 g of this crude was dehydrated by heating to 50 °C for 1 h in $POCl_3$ (8 mL). Quenching in water followed by extraction into CH_2Cl_2 (dried using Na_2SO_4) and rotary evaporation gave a brown oil. Purification by vacuum distillation (50 °C at 10^{-3} atm) gave a colourless oil (0.20 g, 12% from acid). Spectral data match the literature.[30] ^{1}H NMR ($CDCl_3$, 500 MHz): 7.47 (d, J = 5 Hz, 1H), 6.95 (d, J = 5 Hz, 1H), 2.46 (s, 3H). IR (film): 3108 (m), 2926 (m), 2215 (s), 1448 (m), 1404 (m), 1264 (w), 1174 (w), 1086 (w), 1014 (w), 939 (w), 839 (w), 734 (m) cm^{-1}.

Characterization

As shown in Tables 1 and 2, the following products were characterized by comparing the GC retention times of the reaction products with the retention times of commercial or independently synthesized products: **1-Br**, **1-Br$_2$**, **1-I**, **1-I$_2$**, **4-Br**, **4-Br$_2$**, and *o*- and *p*-bromophenol. Peaks for 2- and 4-bromoaniline and 2,4-dibromoaniline were assigned according to the literature method.[18] The following products were assigned by isolating the products from the reaction mixture and comparing with literature NMR spectra: **1-BrI**,[31] **2-Br**,[32] **2-Br$_2$**,[33] **4-I**,[34] **4-I$_2$**,[34] **5-Br**,[35] and 1-bromo-2-naphthol.[36] The following compounds are commercially available and were assigned based on the NMR spectra in the Sigma-Aldrich online spectral database: **3-Br** and 2,6-dibromo-4-nitrophenol. For the unisolable 2-bromo-4-nitrophenol (a material that can be isolated by another method[37]), the product was assigned based on the mass spec and the fact that the dibrominated product contained 2,6-disubstitution and therefore must have gone through this monosubstituted structure. Finally, the regiochemistry of **3-Br$_2$** was never definitively determined (and was never more than a minor product anyway).

Supplementary data

Supplementary data are available with the article through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/cjc-2013-0058. Supplementary data include full characterization data for all compounds, copies of ^{1}H NMR spectra, data for the NBS reactions, and details on the calculations for the green scales.

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