Green halogenation reactions for (hetero)aromatic ring systems in alcohol, water, or no solvent

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ABSTRACT: A new method of brominating aromatic and heteroaromatic ring systems is investigated. The combination of hydrobromic acid as the halogen source; of hydrogen peroxide as the oxidant; and ethanol, water, or no solvent are evaluated as greener conditions than those that have been previously published. The new conditions give high yields and good regioselectivity for a variety of substrates when the ring is activated by electron-donating groups or heteroatoms. Phenols, anisole, thiophenes, and pyrrole give comparable or superior results when compared to a traditional bromination by *N*-bromosuccinimide in tetrahydrofuran. Other nitrogen-containing heterocycles do not react under the conditions because they are protonated and hence deactivated; similarly, substrates with electron-withdrawing groups are not brominated. The reaction is very tolerant of a variety of functional groups.

Keywords

green chemistry

bromination

heterocyclic chemistry

solvent-free synthesis

thiophene

Introduction

Halogenated aromatic compounds are common intermediates in organic synthesis. Ideally, carbon-carbon bonds can be made directly from hydrocarbons;[1] however, as a practical matter, such reactions are in their infancy, and reactions such as those developed by Stille[2] and Suzuki[3] have a wider range of substrates and substitution patterns available to them. Although both of these reactions require a halogenated substrate and (usually[4]) an expensive palladium catalyst to complete the coupling, they continue to be used because of their versatility. In addition to their synthetic uses, halogenated organics have many commercially important applications including flame retardants and pesticides.[5]

Because of this continued need for generating halogenated organic materials,[6] focus has turned to developing more environmentally friendly and sustainable synthetic methods for generating carbon-halogen bonds. Because of our interest in extended π-systems for use as molecular semiconductors,[7-10] we are interested in the halogenation of aromatic rings including heterocyclic systems, and also require a reaction that has high functional group tolerance. Thus, we require a source of Br^+ to effect electrophilic aromatic substitution. Natural, abundant sources of the bromine atom are inorganic bromides, so an oxidant is required,[11] preferably one that is not transition metal-based[12-14] (including a metal catalyst[15]) because trace metals can have a deleterious effect on semiconductor films. Similarly, the oxidant could not be so powerful that it would react with the substrate, *e.g.* oxidizing thiophene to *S*,*S*-dioxothiophene. Oxone[16] and *tert*-butylhydroperoxide[17] were rejected as being atom-uneconomical, while we anticipated purification difficulties with the high boiling point of dimethylsulfoxide (DMSO) in the HBr/DMSO system.[18,19] A very recent report uses an photo-excited catalytic anthraquinone as an oxidant, but this adds complexity to the process.[20] We therefore chose hydrogen peroxide as

the best oxidant:[21-23] it works for both bromination and iodination, it is stable with a variety of functional groups, it does not oxidize the ring sulfurs in thiophene, and its waste biproduct is water. Unfortunately, the published peroxide method uses ammonium salts as the halide source (not atom economical) and acetic acid as solvent (while it can be sustainably sourced, it has a relatively high boiling point).

To address these issues, we present herein an evaluation of "greener" conditions for bromination of aromatic[24] and heteroaromatic substrates, summarized in Scheme 1. We continue to use hydrogen peroxide as the oxidation source, for the reasons given above. Instead of ammonium bromide, we use hydrobromic acid as the source of Br^-, which saves four atoms from the ammonium counterion (and reduces the mass by 1/18). Use of HBr has the added bonus of replacing the acidic proton of acetic acid (rather than using, for example, sodium bromide[25]). As a result, solvents that are more sustainable and/or volatile than acetic acid can be employed, such as ethanol, water, or even elimination of the solvent altogether.[26]

Experimental Section

Substrates were purchased from Sigma-Aldrich and used as received. Hydrobromic acid was 48% w/w from Alfa, hydroiodic acid was 47-50% from Baker, hydrogen peroxide was 30% from Fisher. Gas chromatography (GC) was performed on an Agilent 6850 with a carbowax capillary column and a flame-ionization detector. Nuclear magnetic resonance (NMR) spectra were recorded as $CDCl_3$ solutions on a Varian Unity Inova 500 (^1H at 500 MHz, ^{13}C at 126 MHz) at room temperature; chemical shifts are reported in ppm referenced to TMS added to the solvent.

General synthetic procedure (GC-scale). A mixture of 2.0 mmol of substrate and 2.0 or 4.0 mmol of HX were stirred in solvent (if any) for a few minutes. A 30% solution of H_2O_2 in water was added in a 10% excess relative to the amount of halogen. The mixture was allowed to react for 4 hours. At this time, 0.2 mL of the reaction mixture was worked up by adding to 4.0 mL of water and extracted with 4.0 mL of CH_2Cl_2. The organic layer was separated and dried with sodium sulfate and the solution injected into the GC. A similar procedure was performed after 24 hours of total reaction time.

Preparation of 2,5-dibromothiophene (Table 1, entry 13). Thiophene (2.01 g, 23.9 mmol) and HBr (5.75 mL, 50.7 mmol) were stirred in water while hydrogen peroxide (5.75 mL, 56.3 mmol) was added dropwise over 10 minutes. The mixture was stirred for 24 hours, followed by extraction in dichloromethane, drying over sodium sulfate, and isolation via rotary evaporation. Yield 4.58 g (85%, based on 4:1 ratio of $C_4H_2Br_2S$:C_4H_3BrS determined by NMR peak integration). ^{1}H NMR: δ 6.823 (s, 80% total peak area), 6.858 (dd, J = 5.5 Hz, 4 Hz, 6.7% total peak area), 7.038 (d, J = 3.5 Hz, 6.7% total peak area), 7.212 (d, J = 5.5 Hz, 6.7% total peak area) ppm.

Preparation of 2,5-dibromo-3-methylthiophene (Table 2, entry 27). 3-Methylthiophene (1.00 g, 10.2 mmol) and HBr (2.50 mL, 22.1 mmol) were stirred while hydrogen peroxide (2.50 mL, 24.5 mmol) was added dropwise over 10 minutes. The resultant mixture was stirred for 24 hours, followed by extraction in dichloromethane, drying over sodium sulfate, and isolation via rotary evaporation. Yield 2.43 g (93%). ^{1}H NMR: δ 2.128 (s, 3H), 6.734 (s, 1H) ppm.

Preparation of 4-bromoanisole (Table 2, entry 17). Anisole (2.01 g, 19.7 mmol) and HBr (2.25 mL, 19.9 mmol) were stirred in methanol while hydrogen peroxide (2.25 mL, 22.0 mmol)

was added dropwise over 10 minutes. The resultant mixture was stirred for 24 hours, followed by extraction in dichloromethane, drying over sodium sulfate, and isolation via rotary evaporation. Yield 3.18 g (92%). ^{1}H NMR: δ 3.740 (s, 3H), 6.752 (d, J = 7 Hz, 2H), 7.345 (d, J = 7 Hz, 2H) ppm.

Preparation of 2-bromo-4-*tert*-butylphenol (Table 2, entry 13). 4-*tert*-Butylphenol (1.01 g, 6.7 mmol) and HBr (0.81 mL, 7.2 mmol) were stirred while hydrogen peroxide (0.81 mL, 7.9 mmol) was added dropwise over 10 minutes. The mixture was stirred for 24 hours, followed by extraction in dichloromethane, drying over sodium sulfate, and isolation via rotary evaporation. Yield 1.35 g (88%). ^{1}H NMR: δ 1.266 (s), 6.922 (d, J = 8.5 Hz, 1H), 7.203 (d, J = 8.5 Hz, 1H), 7.446 (s, 1H) ppm. A small peak (8%) at 7.43 ppm indicates the presence of 2,6-dibromo-4-*tert*-butylphenol.

Preparation of 2,6-dibromo-4-*tert*-butylphenol (Table 2, entry 12). 4-*tert*-Butylthiophene (1.00 g, 6.67 mmol) and HBr (1.62 mL, 14.3 mmol) were stirred in ethanol while hydrogen peroxide (1.62 mL, 15.9 mmol) was added dropwise over 10 minutes. The resultant mixture was stirred for 24 hours, followed by extraction in dichloromethane, drying over sodium sulfate, and isolation via rotary evaporation. Yield 1.60 g (70%). ^{1}H NMR: δ 1.268 (s, 9H), 7.427 (s, 2H) ppm.

Results and Discussion

In order to directly compare the new conditions presented herein with the previously published green syntheses using peroxide in acetic acid,[21-23] we chose to look at aromatic compounds containing benzene and thiophene rings with various substituents. Table 1 gives results for brominating unsubstituted rings of various types using the mineral acid in the solvents

given; several brominations of the same substrate using *N*-bromosuccinimide (NBS) in tetrahydrofuran (THF) are shown for comparison. As can be seen, the alcohols methanol and ethanol are generally acceptable solvents. On the other hand, reactions done in water are less successful (with the notable exception of Table 1, entry 13), perhaps due to the fact that the substrates are not soluble, which gives rise to a two-phase reaction.

In cases where the substrate and brominated product are both liquid, Table 1 also gives results for "solvent-free" reactions; of course, these are not completely solvent-free because both the hydrobromic acid and the peroxide are water solutions of 48% and 30% respectively. Neat reactions are considered the most green, since the solvent is usually the largest single contributor to the waste stream. Satisfyingly, the no-added-solvent reactions appear to be very successful in many cases (*e.g.*, Table 1, entry 4; Table 2, entries 18 and 27). Unfortunately, there are practical difficulties in performing these no-added-solvent reactions, which can easily be understood in terms of the mechanism. There is general agreement that the reaction of peroxide with Br^- generates a Br^+ intermediate of the form ROBr,[21] *e.g.*, HOBr in water (or CH_3OBr in methanol, CH_3COOBr in acetic acid, etc.).

$$H_2O_2 + HBr \rightarrow HOBr + H_2O \qquad (1)$$

However, this net reaction hides the fact that it is a two-step process, *i.e.*,

$$2\ HBr + H_2O_2 \rightarrow Br_2 + 2\ H_2O \qquad (1a)$$

$$Br_2 + H_2O \rightarrow HBr + HOBr \qquad (1b)$$

Adding reaction 1a to 1b yields reaction 1. In the case of solvent-free reactions, there is very little water for soaking up the Br_2 (reaction 1b), and we have observed a red haze of gaseous bromine within the reaction vessels, enough in some cases that metal needles inserted in the septum to allow pressure equalization are completely destroyed after 24 hours. The strongly exothermic reaction 1a also causes a rapid temperature rise because there is no solvent to act as a heat reservoir, which exacerbates the problem by pushing the Br_2 into the gas phase. The net result is that we have found that solvent-free reactions require careful monitering, and even if that is done, some reactions are not as regioselective under solvent-free conditions (*e.g.* compare in Table 1, entries 8 and 11 with entry 15). However, in cases where one product is strongly favoured, controlled solvent-free reactions will give the same product in similar yield. Solvent-free reactions where either the substrate or the product is solid gave very poor results in every case and are not included in the tables.

Having established the stability of the ring systems in the reaction conditions, we next investigated functional group tolerance. Table 2 displays the results. As is the case with similar green conditions, electron-withdrawing groups (EWG) prevent bromination, even EWGs as weak as bromo. The acidic conditions cause protonation of nitrogen groups and rings such as aniline, thiazole, and pyridine (but not pyrrole), leading to deactivation of the ring and poor results; the acid-free bromination conditions of Song, *et al.* work better than our conditions for nitrogen-containing heterocycles.[27] On the other hand, most of these substrates are recovered unreacted, suggesting that these functionalities are stable, which is promising for the general use of this reaction on complex molecules. This functional group behaviour is the same as that observed for the previously-published conditions. The following functional groups are stable in the reaction conditions: NO_2, OH, Br and Cl, CHO, CN, and OCH_3; as are the heterocyclic rings

pyridine, thiophene, and thiazole. The benzyl-type methyl group is also stable (Table 2, entries 25 and 27), unlike the HBr-H_2O_2 oxidation in similar conditions of benzyl to phenylaldyhyde.[28]

In order to compare the efficacy and regioselectivity of the green conditions, product distributions were compared to brominations using *N*-bromosuccinimide (NBS) in tetrahydrofuran (THF). Besides being atom-uneconomical and using an organic solvent, NBS reactions have the further disadvantage of succinimide contamination in the resulting product when a simple workup is used (*i.e.* no column); this can be seen in the GC of these reactions. Therefore, our new green conditions are both more atom-economical and less labour intensive than the equivalent traditional bromination reaction. They are also similar in yield and regioselectivity to the traditional NBS/THF reactions, for example comparing reactions 8 with 18 and 42 with 45. In a number of cases, the green conditions are considerably better, especially for benzene (where the THF conditions simply do not work) and phenol (compare Table 2, entries 2 and 8).

The "GC yields" reported in the Tables are simply the ratios of the GC peaks. Because the reactions were worked up with an aqueous extraction before injection into the GC, no water-soluble, involatile, or insoluble biproducts will appear in the chromatograms. Therefore, for several reactions we performed gram-scale isolation reactions to determine the total amount of product; the yields are reported under "notes" in Tables 1 and 2 for selected reactions (chosen from those reactions that were quantitative by GC analysis). We were gratified to find that the isolated yields were generally high and that product purity (by NMR) is very high, especially considering that purification was only by extraction, without column chromatography. One exception was the attempt to scale-up the bromination of neat benzene (Table 1, entry 4), which resulted in very poor isolated yield. This is perhaps not surprising considering the discussion

above, *i.e.*, that the oxidation reaction is very exothermic and the substrate is volatile – we conclude that substrate was lost to evaporation as the reaction heated up. The reaction of thiophene in water (Table 1, entry 13) did not go to completion when scaled up, resulting in a 4:1 ratio of di- to monobromination; the biphasic conditions and the equilibrium between Br_2 and HBr in the presence of water co-conspire to limit the availabilty of Br^+, *i.e.*, an excess of HBr/H_2O_2 or a longer reaction time would be required to drive this scale-up reaction to completion.

As expected, chlorides are not accessible under these conditions. This is due to the limit on the oxidizing power of the peroxide. Unfortunately, iodinations are also not easily done under these conditions. This was an unpleasant surprise, considering that iodine substitution is relatively straightforward on activated rings when the solvent is acetic acid[22,23] (and in the case of pyrazoles, water[29]). Since purple solid collects in the reaction vessel, and since NMR and GC solutions are coloured purple, it is concluded that while the I^- is successfully being oxidized to I_2, analogous to reaction 1a, either the subsequent generation of RO-I (reaction 1b) does not take place or the subsequent iodinization of substrate by RO-I is slow relative to its comproportionation reaction with I^- remaining in the solution. Table 3 shows some representative data. As can be seen by comparing the same substrates in Tables 1 and 2 with their entries in Table 3, in cases where bromination occurs quantitatively and regioselectively, iodination leads to mixtures of products, usually including a significant amount of unreacted substrate.

Conclusion

We have shown that solvent-free bromination of aromatic and heteroaromatic rings is

possible with the green reagent combination of hydrogen peroxide, bromide, and activated substrate. The usual issues with solvent-free reactions apply here, *viz*, the exothermic heat generation and high concentration gives less selectivity than reactions in solvent and solid substrates do not work well. Fortunately, in some of these cases, the reaction is often possible in the solvents methanol, ethanol, or (occasionally) water, which are much greener solvents than those typically used in bromination reactions. Although these conditions do not appear to be general to all halogens, working much better for bromine than iodine or chlorine, the reaction conditions are very forgiving, allowing bromination of a wide variety of ring systems and in the presence of many different functional groups.

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References

(1) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215, DOI: 10.1021/cr100280d.

(2) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636, DOI: 10.1021/ja00479a077.

(3) Miyaura, N.; Suzuki, A. *J. Chem. Soc. Chem. Commun.* **1979**, 866, DOI: 10.1039/C39790000866.

(4) Chan, T. L.; Wu, Y.; Choy, P. Y.; Kwong, F. Y. *Chem. Eur. J.* **2013**, *19*, 15802, DOI: 10.1002/chem.201301583.

(5) Yoffe, D.; Frim, R.; Ukeles, S. D.; Dagani, M. J.; Barda, H. J.; Benya, T. J.; Sanders, D. C. *Ullmann's Encyclopedia of Organic Chemistry: Bromine Compounds*; Wiley-VCH Verlag GmbH & Co. KGaA, 2013.

(6) Saikia, I.; Borah, A. J.; Phukan, P. *Chem. Rev.* **2016**, *116*, 6837, DOI: 10.1021/acs.chemrev.5b00400.

(7) Sears, W. A.; Sears, W. M.; MacKinnon, C. D. *Synth. Met.* **2008**, *158*, 50, DOI: 10.1016/j.synthmet.2007.12.002.

(8) Morgan, I. S.; D'Aleo, D. N.; Hudolin, M. L.; Chen, A.; Assoud, A.; Jenkins, H. A.; MacKinnon, C. D. *J. Mater. Chem.* **2009**, *19*, 8162, DOI: 10.1039/B908869E.

(9) Sears, W. A.; MacKinnon, C. D.; Mawhinney, R. C.; Sinnemaki, L. C.; Johnson, M. J.; Winter, A. J.; Robertson, C. M. *Can. J. Chem.* **2010**, *88*, 309, DOI:

doi.org/10.1139/V09-165.

(10) Sears, W. M.; MacKinnon, C. D.; Kraft, T. M. *Synth. Met.* **2011**, *161*, 1566, DOI: 10.1016/j.synthmet.2011.05.020.

(11) Podgoršek, A.; Zupan, M.; Iskra, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 8424, DOI: 10.1002/anie.200901223.

(12) Dinesh, C. U.; Kumar, R.; Pandey, B.; Kumar, P. *J. Chem. Soc. Chem. Commun.* **1995**, 611, DOI: 10.1039/C39950000611.

(13) Choudary, B. M.; Reddy, P. N. *Synlett* **1994**, 450, DOI: 10.1055/s-1994-22886.

(14) Gayakwad, E. M.; Patil, V. V.; Shankarling, G. S. *Environ. Chem. Lett.* **2017**, *15*, 459, DOI: 10.1007/s10311-017-0606-6.

(15) Huang, Z.; Li, F.; Chen, B.; Lu, T.; Yuan, Y.; Yuan, G. *ChemSusChem* **2013**, *6*, 1337, DOI: 10.1002/cssc.201300289.

(16) Firouzabadi, H.; Iranpoor, N.; Kazemi, S. *Can. J. Chem.* **2009**, *87*, 1675, DOI: 10.1139/V09-125.

(17) Barhate, N. B.; Gajare, A. S.; Wakharkar, R. D.; Bedekar, A. V. *Tetrahedron Lett.* **1998**, *39*, 6349, DOI: 10.1016/S0040-4039(98)01305-7.

(18) Song, S.; Li, X.; Sun, X.; Yuan, Y.; Jiao, N. *Green Chem.* **2015**, *17*, 3285, DOI: 10.1039/C5GC00528K.

(19) Liu, C.; Dai, R.; Yao, G.; Deng, Y. *J. Chem. Res.* **2014**, *38*, 593, DOI: 10.3184/174751914X14114780483352.

(20) Petzold, D.; König, B. *Adv. Synth. Catal.* **2018**, *360*, 626, DOI: 10.1002/adsc.201701276.

(21) Krishna Mohan, K. V. V.; Narender, N.; Srinivasu, P.; Kulkarni, S. J.; Raghavan, K. V. *Synth. Commun.* **2004**, *34*, 2143, DOI: 10.1081/SCC-120038491.

(22) Narender, N.; Suresh Kumar Reddy, K.; Krishna Mohan, K. V. V.; Kulkarni, S. J. *Tetrahedron Lett.* **2007**, *48*, 6124, DOI: 10.1016/j.tetlet.2007.06.138.

(23) D'Aleo, D. N.; Allard, S. R.; Foglia, C. F.; Parent, S. L. M.; Rohr, D. J.; Gottardo, C.; MacKinnon, C. D. *Can. J. Chem.* **2013**, *91*, 679, DOI: 10.1139/cjc-2013-0058.

(24) Barhate, N. B.; Gajare, A. S.; Wakharkar, R. D.; Bedekar, A. V. *Tetrahedron* **1999**, *55*, 11127, DOI: 10.1016/S0040-4020(99)00628-6.

(25) Halder, J. *Rasayan J. Chem.* **2012**, *5*, 183.

(26) Kerton, F. M.; Marriott, R. *Alternative Solvents for Green Chemistry*; 2 ed.; Royal Society of Chemistry, 2013.

(27) Song, S.; Sun, X.; Li, X.; Yuan, Y.; Jiao, N. *Org. Lett.* **2015**, *17*, 2886, DOI: 10.1021/acs.orglett.5b00932.

(28) Ghaffarzadeh, M.; Bolourtchian, M.; Tabar-Heydar, K.; Daryaei, I.; Mohsenzadeh, F. *J. Chem. Sci.* **2009**, *121*, 177, DOI: 10.1007/s12039-009-0020-0.

(29) Kim, M. M.; Ruck, R. T.; Zhao, D.; Huffman, M. A. *Tetrahedron Lett.* **2008**, *49*, 4026, DOI: 10.1016/j.tetlet.2008.04.082.

Table 1: Bromination of unsubstituted aromatic rings using various conditions

entry	substrate	halide source, halide: substrate ratio	solvent[a]	time /h	results and reaction selectivity[b]			
					unreacted substrate	mono-Br product	di-Br product	notes
1	benzene	HBr, 2:1	ethanol	24	0	~50	trace	multiple others
2	benzene	HBr, 2:1	methanol	4	30	65	5	many peaks after 24h
3	benzene	HBr, 2:1	water	24	0	~50	trace	multiple others
4	benzene	HBr, 1:1	-	4	0	99	0	
5	benzene	HBr, 2:1	-	4	0	99	0	
6	benzene	NBS, 2:1	THF	24	0	trace	10	many products
7	thiophene	HBr, 1:1	ethanol	4	18	78	4	
8	thiophene	HBr, 2:1	ethanol	24	0	0	99	
9	thiophene	NH_4Br, 2:1	ethanol	120	85	15	0	
10	thiophene	HBr, 1:1	methanol	24	14	84	trace	
11	thiophene	HBr, 2:1	methanol	24	trace	0	99	
12	thiophene	HBr, 1:1	water	24	0	36	64	
13	thiophene	HBr, 2:1	water	24	0	0	99	85% isolated 4:1TBr_2:TBr[c]
14	thiophene	HBr, 1:1	-	4	29	42	30	
15	thiophene	HBr, 2:1	-	4	0	18	82	
16	thiophene	HBr, 3:1	-	4	0	0	50	also 50% tribromo
17	thiophene	NBS, 1:1	THF	4	0	91	9	
18	thiophene	NBS, 2:1	THF	24	0	2	90	multiple small add[n] products
19	pyrrole	HBr, 1:1	ethanol	4	6	82	11	
20	pyrrole	HBr, 2:1	ethanol	4	0	trace	99	trace tribromo
21	pyrrole	HBr, 1:1	methanol	4	43	34	23	long rxn time gives a solid[d]
22	pyrrole	HBr, 2:1	methanol	4	0	0	63	two higher mass peaks
23	pyrrole	HBr, 1:1	water	4	0	0	0	solid[d]
24	pyrrole	HBr, 1:1	-	-	0	0	0	precipitates as C_4H_6NBr
25	pyridine	HBr, 1:1	ethanol	24	100	0	0	no rxn
26	pyridine	HBr, 1:1	water	24	100	0	0	no rxn
27	pyridine	HBr, 1:1	-	24	100	0	0	no rxn
28	furan	HBr, 1:1	ethanol	4	0	0	35	many products
29	furan	HBr, 2:1	ethanol	4	0	0	55	many products
30	furan	HBr, 2:1	-	24	0	0	66	many products 5-10%

notes: [a] "-" Indicates no solvent. [b] Relative quantities of residual substrate and product(s) were determined by peak area integration in GC traces. Calibration was not performed, and detector response was not calibrated to quantify peak volumes; therefore, GC yields were not determined. [c] Relative yield from isolation reaction characterized by NMR peak integrations. [d] Presumably a polymerization product

Table 2: Bromination of substituted aromatics and heteroaromatics

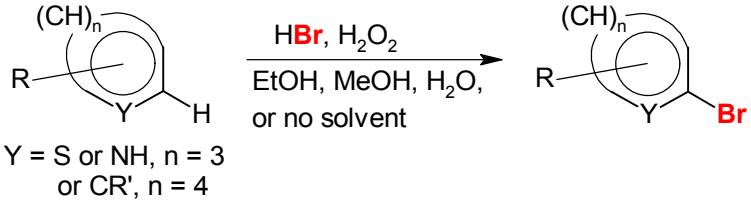
entry	substrate	halide source, substrate: halide ratio	solvent	time	results and reaction selectivity[a]			
					unreacted substrate	mono-Br product	di-Br product	notes
1	toluene	HBr, 1:1	EtOH	24	0	trace	trace	many peaks, incl. benzyl[b]
2	phenol	HBr, 1:1	EtOH	4	11	65 *para* 24 *ortho*	0	
3	phenol	HBr, 2:1	EtOH	4	trace	23 *para*	66 (2,4) 2 (2,6)	9 tri-Br
4	phenol	HBr, 1:1	MeOH	24	0	73 *para* 18 *ortho*	8 (2,4) 1 (2,6)	
5	phenol	HBr, 2:1	MeOH	24	0	6 *para*	66 (2,4) trace 2,6	28 tri-Br
6	phenol	HBr, 1:1	water	24	25	75 *para* 23 *ortho*	1 (2,4)	
7	phenol	HBr, 2:1	water	24	0	3 *para*	86 (2,4 4(2,6)	8 tri-Br
8	phenol	NBS, 1:1	THF	4	39	25 *para* 12 *ortho*	8 (2,4) ~1 (2,6)[c]	14 tri-Br
9	phenol	NBS, 2:1	THF	24	trace	22 *para* trace *o*	33 (2,4) ~1 (2,6)[c]	44 tri-Br
10	2-Br-phenol	HBr, 1:1	EtOH	24	7	66 (2,4) 10 (2,6)	16	
11	*p*-tBu-phenol	HBr, 1:1	EtOH	24	0	99	0	Br,OH *ortho*[d]
12	*p*-tBu-phenol	HBr, 2:1	EtOH	24	0	0	99	Br,OH *ortho* 70% isolated[d]
13	*p*-tBu-phenol	HBr, 1:1	EtOH	24	trace	91	8	88% isolated[d]
14	*p*-tBu-phenol	NBS, 1:1	THF	4	42	22	35	no change after 24h
15	*p*-tBu-phenol	NBS, 2:1	THF	24	0	trace	99	
16	anisole	HBr, 1:1	EtOH	24	23	77 *para*		
17	anisole	HBr, 1:1	MeOH	24	0	99 *para*	0	92% isolated[d]
18	anisole	HBr, 1:1	-	24	7	93 *para*	0	
19	anisole	HBr, 2:1	-	24	0	30 *para*	70	
20	anisole	NBS, 1:1	THF	24	1	99 *para*	0	
21	anisole	NBS, 2:1	THF	4	0	99 *para*	trace	
22	benzaldehyde	HBr, 2:1	-	24	67	33	0	
23	nitrobenzene	HBr, 1:1	EtOH	24	100	0	0	
24	nitrobenzene	HBr, 1:1	water	24	100	0	0	
25	3-MeT	HBr, 1:1	EtOH	4	4	96	0	[d]
26	3-MeT	HBr, 1:1	-	4	0	84	15	
27	3-MeT	HBr, 2:1	-	24	0	0	98	1% tri-Br 93% isolated[d]
28	3-MeT	NBS, 1:1	THF	4	trace	99	trace	
29	3-MeT	NBS, 2:1	THF	4	0	33	66	
30	2-TI	HBr, 1:1	-	24	0	69	0	31% di-Br
31	2,2'-bithiophene	HBr, 2:1	water	24	trace	22	68	10% tri-Br
32	1,3-thiazole	HBr, 1:1	water	24	99	1	0	
33	thianaphthene	HBr, 1:1	EtOH	20	46	54	0	
34	benzofuran	HBr, 1:1	water	24	81	19	0	

notes: [a] Relative quantities of residual substrate and product(s) were determined by peak area integration in GC traces. Calibration was not performed, and detector response was not calibrated to quantify peak volumes; therefore, GC yields were not determined. [b] NMR confirms the presence of benzyl substitution. [c] This product overlaps with succinimide. [d] Relative yield from isolation reaction characterized by NMR peak integrations.

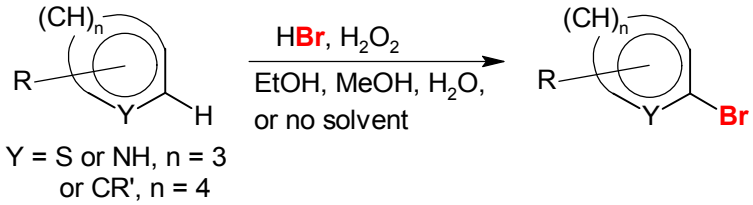
Table 3: Iodination reactions

entry	substrate	halide source, substrate: halide ratio	solvent	time	results and reaction selectivity[a]		
					unreacted substrate	1:1 product	2:1 product
1	benzene	HI, 2:1	EtOH	24	100	0	0
2	anisole	HI, 1:1	EtOH	24	100	0	0
3	*p*-tBu-phenol	HI, 2:1	EtOH	24	2	17	82
4	thiophene	HI, 2:1	EtOH	24	3	19	78
5	thiophene	HI, 2:1	MeOH	24	42	58	0
6	thiophene	HI, 2:1	water	24	21	79	0
7	thiophene	HI, 2:1	-	24	trace	5	94
8	thiophene	NIS, 2:1	THF	24	0	6	87

Scheme 1



Describing greener conditions than previously reported for the bromination of aromatic and heteroaromatic rings, including a solvent-free option for liquid substrates.



Y = S or NH, n = 3
or CR', n = 4