Electrophilic Aromatic Bromination Using Bromodimethylsulfonium Bromide Generated in Situ†

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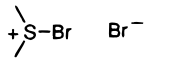
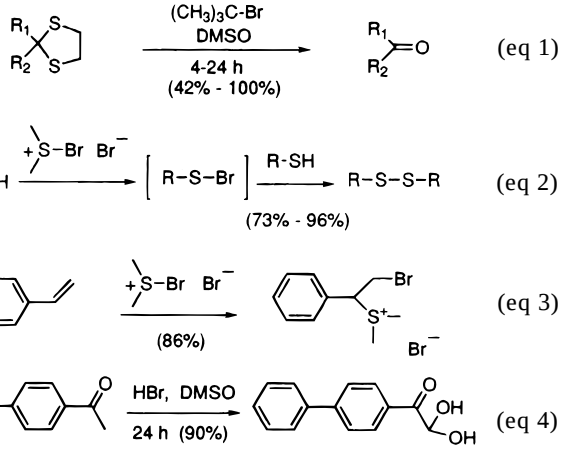
It has been shown that bromodimethylsulfonium bromide, generated *in situ* by treating dimethyl sulfoxide with aqueous hydrobromic acid, is a milder and more selective reagent for electrophilic aromatic bromination than elemental bromine.

Positive halogenating agents,[1] such as bromodimethylsulfonium bromide (**1**), are useful synthetic reagents because of their ease of preparation[2−7] and the wide variety of transformations they facilitate. For example,



bromodimethylsulfonium bromide (**1**)

in 1979, Olah and co-workers reported that the cleavage of thioketals[3] (eq 1) and the oxidative coupling of thiols[8] (eq 2) can be achieved with bromodimethylsulfonium bromide. The addition of **1** across olefinic bonds to produce sulfonium bromides has also been observed (eq 3).[4] The oxidation of acetophenones to glyoxal hydrates can be achieved with **1** generated *in situ* from aqueous hydrobromic acid in DMSO (eq 4).[9] Floyd and co-workers observed electrophilic aromatic bromination as a side reaction in several of these oxidations. Under these conditions, others have also observed aromatic bromination using bromodimethylsulfonium bromide generated *in situ*. Of particular note is the pioneering work of Megyeri and Keve,[7] in which indole alkaloids were halogenated using reagent **1** (eq 5). During an investigation of alkylation reactions, Fletcher and Pan noted the



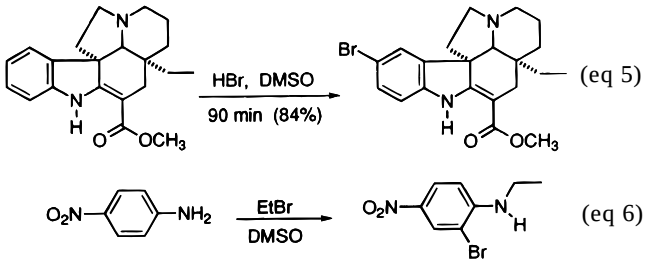
(eq 1)

(eq 2)

(eq 3)

(eq 4)

bromination of three aromatic amines on heating with ethyl bromide in DMSO; an example is shown in eq 6.[10]



(eq 5)

(eq 6)

Despite the broad synthetic utility of bromoarenes, their preparation using bromodimethylsulfonium bromide has not been systematically investigated. We therefore undertook a study to establish the scope and limitations of this bromination procedure and to compare it to existing methods.

Results and Discussion

Unactivated arenes, such as benzene, toluene, or 2-methylnaphthalene,[11] do not react with **1**; hence, an aromatic ring activated by an electron-donating group was used to optimize the experimental conditions. We found that the addition of a large excess of commercial 48% aqueous HBr (>40 equiv) to a solution of 2-methoxynaphthalene (**2**) in DMSO at room temperature gave 1-bromo-2-methoxynaphthalene (**3**) in nearly quantitative

† Taken in part from the Ph.D. Dissertation of Rodgers Hicks, The University of Georgia, 1996.

⊗ Abstract published in *Advance ACS Abstracts,* June 1, 1997.

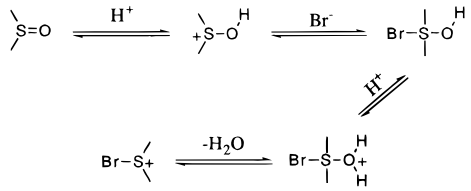
(1) (a) *Electrophilic Halogenation: Reaction Pathways Involving Attack by Electrophilic Halogens on Unsaturated Compounds*; de la Mare, P. B. D., Ed.; Cambridge University Press: London, 1976. (b) Berliner, E. *J. Chem. Ed.* **1996**, *43*, 124.

(2) Bromodimethylsulfonium bromide may be prepared *in situ* from dimethyl sulfide and elemental bromine,[3,4] by the treatment of dimethyl sulfoxide with aqueous hydrobromic acid,[5,6] or by the treatment of dimethyl sulfoxide with trimethylsilyl bromide.[7]

(3) Olah, G.; Vankar, D.; Arvanaghi, M.; Prekash, G. *Synthesis* **1979**, 720.

(4) Chow, Y.; Baker, B. *Synthesis* **1982**, 648.

(5) The following mechanism accounts for the formation of bromosulfonium bromide from DMSO and HBr; see: Mislow, K.; Simmons, T.; Melillo, J.; Ternay, A. *J. Am. Chem. Soc.* **1964**, *86*, 1452.



(6) Landini, D.; Montari, F. *J. Chem. Soc., Chem. Commun.* **1968**, 86.

(7) Megyeri, G.; Keve, T. *Synth. Commun.* **1989**, *19*, 3415.

(8) Olah, G.; Arvanaghi, M.; Vankar, Y. *Synthesis* **1979**, 721.

(9) Floyd, M.; Du, M.; Fabio, P.; Jacob, L.; Johnson, B. *J. Org. Chem.* **1984**, *50*, 5022.

(10) Fletcher, T.; Pan, H. *J. Am. Chem. Soc.* **1956**, *78*, 4812.

(11) Although 2-methylnaphthalene failed to react with **1**, even with heating, it reacted slowly with elemental bromine to give 1-bromo-2-methylnaphthalene as well as other inseparable byproducts.

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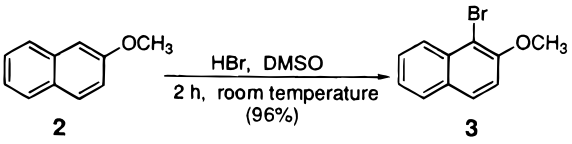
Table 1

solvent	reaction condns	yield of 3 (%)	reaction completion
DMSO	2 h at rt	96	complete
acetonitrile	32 h at rt	84	trace unreacted **2**
THF	1 h at reflux	trace	only unreacted **2**
THF	24 h at reflux	99	complete
THF/AcOH (3:1)	2 h at rt	50	~50% complete
AcOH/DMSO (2:1)	<5 min	96	complete

yield within 2 h (eq 7). Treating **2** with 2−20 equiv of HBr also produces bromide **3**; however, these reactions require longer reaction times in order to reach completion. A large excess of HBr is therefore used to minimize reaction times.



2 **3** (eq 7)

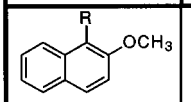
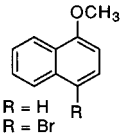
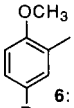
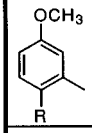
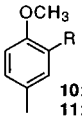
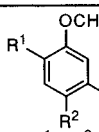
The results of the bromination of **2** with aqueous hydrobromic acid and dimethyl sulfoxide in other cosolvents are summarized in Table 1. Bromination is slow in acetonitrile and very sluggish in THF; only a trace of bromide **3** was obtained after 1 h in refluxing THF. However, the use of acetic acid as a cosolvent greatly enhances the reaction rate. This observation is consistent with the ionic nature of the electrophilic reagent **1**, which is better solvated and stabilized in a polar medium.

We have established two general protocols for aromatic bromination with bromodimethylsulfonium bromide generated *in situ*. The addition of aqueous hydrobromic acid to a solution of the substrate in DMSO is hereafter referred to as general procedure A. In general procedure B, the DMSO is added to a solution of the substrate in acetic acid and aqueous hydrobromic acid. Six aryl methyl ethers were brominated by using general procedures A and B and with bromine in carbon tetrachloride (general procedure C)[12] or in acetic acid (general procedure D)[13] (Table 2). In each of these examples, the bromodimethylsulfonium bromide-based procedures gave the expected monobromides free of side products. In contrast, the use of bromine with *o*-cresol (**6**) produces the benzylic bromide, via a free-radical process, while substrates **4** and **8** gave large quantities of dibromides. In the case of *m*-dimethoxybenzene (**12**), the formation of dibromide **14** was unavoidable using any conditions other than reagent **1** and short reaction times.

Phenols and anilines also react with bromodimethylsulfonium bromide generated using 48% aqueous hydrobromic acid (Table 3). Normally, the bromination of aniline in aqueous solvents provides large amounts of the tribromoaniline product independent of the stoichiometry of the halogen employed. However, polybromination was not observed when either aniline (**20**) or *N*,*N*-dimethylaniline (**22**) was treated with bromodimethylsulfonium bromide. Twenty grams of 2-methoxynaphthalene (**2**) and 2-isopropylphenol (**15**) were brominated in excellent yield by using general procedures A and B, demonstrating the utility of this methodology on a preparative scale.

(12) Adams, R.; Marvel, C. S. *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. I, p 128.
(13) Reference 1a, p 126.

Table 2

Substrate / Product	Percent Yield and Reaction Time Using Standard Conditions			
	HBr, DMSO "A"	HBr, AcOH, DMSO "B"	Br_2, CCl_4 "C"	Br_2, AcOH "D"
 **2**: R = H **3**: R = Br	96% of **3** after 2-h	96% of **3** after 5-min	90% of **3** after 5-min	89% of **3** after 5-min
 **4**: R = H **5**: R = Br	77% of **5** after 72-h	97% of **5** after 24-h	90% of **5** after 72-h	85%[a] of **5** after 72-h
 **6**: R = H **7**: R = Br	82% of **7** after 12-h	86% of **7** after 12-h	75% of **7** after 5-min	75% of **7** after 2-h
 **8**: R = H **9**: R = Br	91% of **9** after 12-h	90% of **9** after 12-h	68%[a] of **9** after 20-min	89%[a] of **9** after 20-min
 **10**: R = H **11**: R = Br	77% of **11** after 72-h	75% of **11** after 72-h	74% of **11** after 20-min	91% of **11** after 5-min
 **12**: $R^1 = R^2 = H$ **13**: $R^1 = H$; $R^2 = Br$ **14**: $R^1 = R^2 = Br$	34% of **13** after 5-min 89% of **14** after 20-min	73% of **14** after 5-min 87% of **14** after 20-min	80%[a] of **14** after 5-min	77% of **14** after 5-min

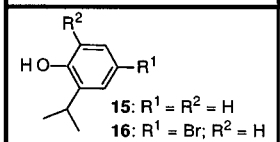
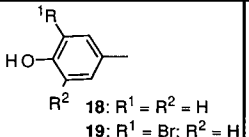
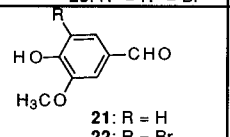
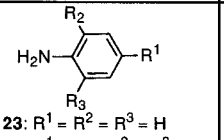
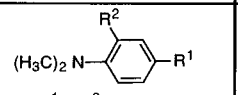
[a] Product contained inseparable impurities. The yield shown is based on analysis of the ^1H NMR spectrum.

The presence of HBr in this bromination procedure and the need for the aromatic system to be electron-rich dictate several limitations. Acid-sensitive functionality, such as acetals or ketals, undergo deprotection before bromination of the arene occurs. Arenes with electron-withdrawing substituents, such as a carboxylic acid group, a nitro group, a halogen substituent, an aldehyde, a ketone devoid of α-protons (such as benzophenone), or an ester moiety, fail to react with **1** even under forcing conditions, while acetophenones produce α-bromo ketones rather than aromatic bromides.

Furans, even those with electron-withdrawing substituents, typically exhibit high reactivity toward halogenation. Nevertheless, bromination was not observed when 2-furoic acid, α-acetylfuran, or furfuraldehyde were treated with bromodimethylsulfonium bromide. Pyridine reacts with mineral acids to form a salt that deactivates the arene toward electrophilic attack so the halogenation of pyridine generally requires forcing conditions. Thus, we were not surprised that pyridine does not react with the bromodimethylsulfonium bromide even under forcing conditions (i.e., prolonged reflux). Efforts to brominate thioanisole with **1** also failed despite a wide variety of experimental conditions.

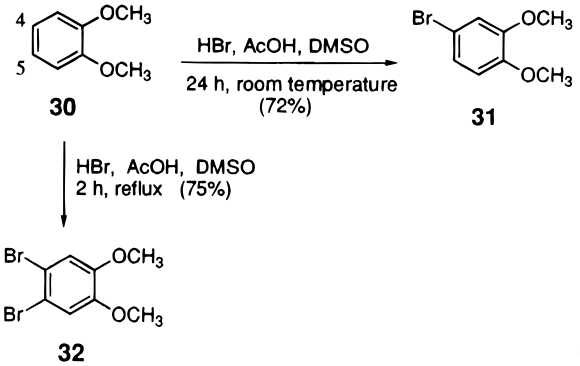
The failure of *m*-dimethoxybenzene (**12**) to undergo

Table 3

Substrate / Product	Percent Yield and Reaction Time Using Standard Conditions			
	HBr, DMSO "A"	HBr, AcOH, DMSO "B"	Br_2, CCl_4 "C"	Br_2, AcOH "D"
 **15**: $R^1 = R^2 = H$ **16**: R^1 = Br; $R^2 = H$ **17**: $R^1 = R^2$ = Br	90% of **16** after 24-h	91% of **16** after 5-min	23% of **16** and 64% of **17** after 5-min	63% of **16** and 31% of **17** after 5-min
 **18**: $R^1 = R^2 = H$ **19**: R^1 = Br; $R^2 = H$ **20**: $R^1 = R^2$ = Br	88% of **19** after 48-h	87% of **19** after 2-h	87% of **19** after 30-min	83% of **19** after 30-min; trace **20**
 **21**: R = H **22**: R = Br	72% of **22** after 12-h	57% of **22** after 12-h	48% of **22** after 24-h	80% of **22** after 20-min
 **23**: $R^1 = R^2 = R^3 = H$ **24**: R^1 = Br; $R^2 = R^3 = H$ **25**: $R^1 = R^2$ = Br; $R^3 = H$ **26**: $R^1 = R^2 = R^3$ = Br	76% of **24** after 6-h	74% of **24** after 24-h	19% of **24**; 33% of **25** and 30% of **26** after 5-min	21% of **24**; 41% of **25** and 31% of **26** after 5-min
 **27**: $R^1 = R^2 = H$ **28**: R^1 = Br; $R^2 = H$ **29**: $R^1 = R^2$ = Br	43% of **28** after 24-h	42% of **28** after 24-h	60% of **28** after 5-min	68% of **28** and 29% of **29** after 5-min

[a] Inseparable byproducts were observed. The yield shown is based on analysis of the ^1H NMR data.

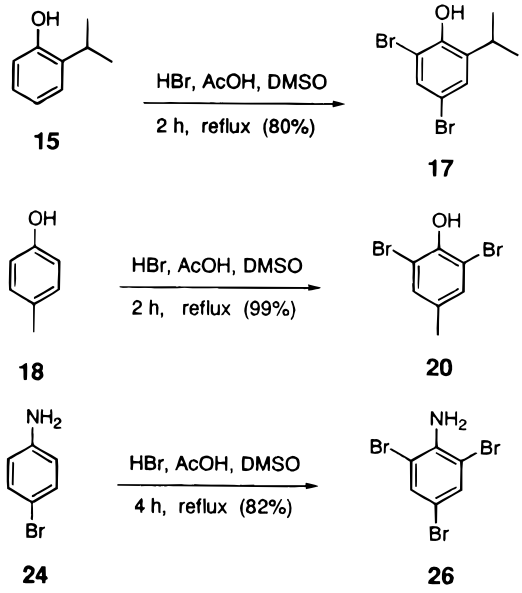
selective monobromination using reagent **1** prompted us to study the reaction with veratrole (**30**) (eq 8). The



30 **31** **32** (eq 8)

activated "4" and "5" positions of veratrole have an *ortho*-relationship; thus, the introduction of an electron-withdrawing halogen at either of these positions will reduce the activity of the second methoxy group. Given the mildness of our bromination procedure, it was not surprising that only monobromination occurs at room temperature, while a second bromine is introduced upon heating. Treatment of veratrole with bromine under conditions C and D afforded inseparable mixtures of bromides **31** and **32** in the ratio of 2:3 and 3:7, respectively.

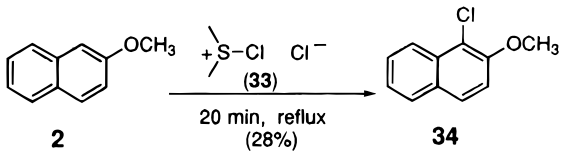
Equation 9 presents three additional examples in which the reaction temperature governs whether mono- or dibromination occurs. Treatment of phenol **15** with



15 **17** **18** **20** **24** **26** (eq 9)

warm HBr, DMSO, and AcOH produces dibromide **17** in good yield (cf. **15** → **16**), whereas bromine in conditions C and D gave a mixture of bromides **16** and **17**. Likewise, bromination of *p*-cresol or aniline using the standard conditions at room temperature gives exclusively the monobrominated product, whereas the same reactions at elevated temperatures result in nearly quantitative yields of dibromide **24** or **25**, respectively.

Although aryl chlorides are less synthetically useful than the corresponding bromides, we were curious to see whether aryl chlorides could be prepared by generating chlorodimethylsulfonium chloride (**33**) *in situ*.[14,15] 2-Methoxynaphthalene was treated using general procedure B, except that aqueous hydrochloric acid was substituted for hydrobromic acid (eq 10). Unfortunately, chlorination was not observed at room temperature, and heating the reaction to reflux gave a poor yield of 1-chloro-2-methoxynaphthalene (**34**).



2 **34** (eq 10)

These results indicate that bromodimethylsulfonium bromide is a milder reagent for electrophilic aromatic bromination than solutions of bromine. Its greater selectivity makes it the reagent of choice for the selective bromination of electron-rich arenes. Moreover, the *in situ* generation of bromodimethylsulfonium bromide using HBr and DMSO eliminates the need to handle the highly toxic and corrosive bromine as well as the use of carbon tetrachloride as the reaction medium.[16]

Experimental Section

General Procedures. Standard ethereal workup consisted of the following procedure: The reaction was cautiously quenched with saturated aqueous sodium bicarbonate. Vola-

(14) For the reactions of **31** with epoxides and enamines, see: Olah, G. A.; Vankar, Y. D.; Arvanaghi, M. *Tetrahedron Lett.* **1979**, *38*, 3653.

(15) Attempts to extend this methodology for the preparation of aryl iodides failed as the iododimethyl sulfonium iodide, generated *in situ*, rapidly decomposes to produce molecular iodine.

tile organic solvents were removed under reduced pressure on a rotary evaporator, and the residue was taken up in ether, washed with brine, and dried over anhydrous magnesium sulfate. Filtration, followed by concentration on a rotary evaporator and at 1 Torr to constant weight, provided a crude residue that was purified by flash chromatography using NM silica gel 60 (230−400 mesh ASTM) and distilled reagent-grade solvents. Proton spectra were obtained in $CDCl_3$, except as noted, and were calibrated using trace $CHCl_3$ present (δ 7.26) as an internal reference.

Chemical Abstracts Service (CAS) registry numbers have been provided by the authors for known reaction products.

General Procedure A: Bromination with HBr/DMSO. To a stirred solution of 500 mg of the substrate in DMSO (15 mL) was added 5 mL of 48% aqueous HBr dropwise. The reaction progress was monitored by TLC analysis. Heat was applied only if the reaction required stirring at rt for more than 3 days to reach completion. The product was isolated using ethereal workup.

General Procedure B: Bromination with HBr/DMSO in Acetic Acid. To a stirred solution of 500 mg of the substrate in AcOH (10 mL) was added 15 mL of 48% aqueous HBr. DMSO (5 mL) was added dropwise, and the reaction progress was monitored by TLC analysis. Heat was applied only if the reaction was sluggish. The product was isolated using ethereal workup.

General Procedure C: Bromination with Bromine in Carbon Tetrachloride.[12] To a stirred solution of 500 mg of the substrate in CCl_4 (6 mL) was added dropwise a 1.0 M solution of bromine in CCl_4 (2.0 equiv relative to the substrate) over a 2-min period. The reaction progress was monitored by TLC analysis. The product was isolated using ethereal workup.

General Procedure D: Bromination with Bromine in Acetic Acid.[13] To a stirred solution of 500 mg of the substrate in AcOH (6 mL) was added dropwise a 1.0 M solution of bromine in CCl_4 (2.0 equiv relative to the substrate) over a 2-min period. The reaction progress was monitored by TLC analysis. The product was isolated using standard ethereal workup.

Bromination of 2-Methoxynaphthalene (2) Using Various Stoichiometries of HBr. Four identical solutions were prepared, each containing 500 mg (3.16 mmol) of **2** in a mixture of 10 mL of acetic acid and 5 mL of DMSO except that 7.5 mL (66.0 mmol) of 48% aqueous HBr was added to the first solution, 3.75 mL of 48% aqueous HBr (33.0 mmol) was added to the second solution, 1.5 mL (13 mmol) of 48% aqueous HBr was added to the third solution, and 0.75 mL (6.60 mmol) of 48% aqueous HBr was added to the fourth solution. Each reaction was monitored by TLC analysis. The 2-methoxynaphthalene in the first solution using 20.88 equiv of HBr was completely brominated within a 35-min period in "quantitative yield" on the basis of NMR analysis. In the second reaction, using 10.44 equiv of HBr, naphthalene **2** was brominated in approximately 60% yield after 30 min on the basis of NMR analysis. In the third experiment, using 1.50 equiv of HBr, naphthalene **2** was brominated in 33% yield after 35 min on the basis of NMR analysis. In the fourth reaction, using 2.08 equiv of HBr, naphthalene **2** was brominated in 15% yield after 35 min on the basis of NMR analysis.

Bromination of 2 in Acetonitrile. To a stirred solution of 500 mg of 2-methoxynaphthalene (**2**) (3.20 mmol) in acetonitrile (15 mL) was added 5 mL of aqueous HBr (57 mmol of a 48% solution), followed by the dropwise addition of 5 mL of DMSO (70.00 mmol). The resulting mixture was stirred at rt for 32 h. Standard ethereal workup, followed by chromatography (elution with H:E, 5:1), gave 4 mg of unreacted **2** and 640 mg (84%) of 1-bromo-2-methoxynaphthalene (**3**) [3401-47-6], which was homogeneous on the basis of TLC analysis (H:E, 1:1, R_f **2** = 0.85, R_f **3** = 0.67).

Bromination of 2 in THF. To a stirred solution of 500 mg of **2** (3.2 mmol) in THF (15 mL) was added 5 mL of aqueous HBr (57 mmol of a 48% solution), followed by the dropwise addition of 5 mL of DMSO (70.00 mmol). The resulting mixture was refluxed for 24 h. An aliquot was withdrawn for ^{1}H NMR analysis and was found to contain unreacted **2** and a trace of bromide **3**. Heating was continued for 1 day. Standard ethereal workup and chromatography (H:E, 20:1 gradient elution to 5:1) gave 759 mg (99%) of **3**.

Bromination of 2 in THF/AcOH. To a stirred solution of 500 mg of **2** (3.20 mmol) in THF (15 mL) was added 5 mL of aqueous HBr (57.00 mmol of a 48% solution) and AcOH (5 mL), followed by the dropwise addition of 5 mL of DMSO (70.00 mmol). The resulting mixture was stirred at rt for 2 h. Standard ethereal workup gave a mixture of **3** (<50% by ^{1}H NMR analysis) and unreacted substrate **2**.

Bromination of 2 Using Conditions A. A reaction mixture containing 500 mg of **2** (3.20 mmol) was stirred at rt for 2 h using general procedure A. Standard ethereal workup, followed by chromatography (elution with H:E, 20:1 gradient elution to 5:1), provided 720 mg (96%) of bromide **3**.

Large-Scale Bromination of 2 Using Conditions A. To a stirred solution of 20.00 g (0.15 mol) of **2** in AcOH (400 mL) and DMSO (100 mL) was added 600 mL of a 48% aqueous solution of HBr (5.30 mol) over a 5-min period. Analysis by TLC indicated the reaction was complete after stirring for 5 min at rt. Standard ethereal workup, followed by recrystallization from ethanol, furnished 27.9 g (93%) of bromide **3**.

Large-Scale Bromination of 2 Using Conditions B. To a stirred solution of 20.00 g (0.15 mol) of **2** in AcOH (200 mL) was added 100 mL of aqueous HBr (88 mmol of a 48% solution), followed by the dropwise addition of 100 mL of DMSO (1.40 mol). Analysis by TLC indicated the reaction was complete after 5 min at rt. Standard ethereal workup, followed by chromatography (elution with H:E, 5:1), furnished 28.05 g (96%) of bromide **3**.

Bromination of 2 Using Conditions C. A reaction mixture containing 500 mg of **2** (3.20 mmol) was stirred at rt for 5 min using general procedure C. Standard ethereal workup, followed by chromatography (elution with H:E, 5:1), provided 675 mg (90%) of bromide **3**.

Bromination of 2 Using Conditions D. A reaction mixture containing 500 mg of **2** (3.20 mmol) was stirred at rt for 5 min using general procedure D. Standard ethereal workup and chromatography (elution with H:E, 20:1 gradient elution to 5:1) provided 668 mg (89%) of bromide **3**.

Bromination of 1-Methoxynaphthalene (4) Using Conditions A. A reaction mixture containing 500 mg of 1-methoxynaphthalene (**4**) (3.20 mmol) was stirred at rt for 72 h using general procedure A. Standard ethereal workup, followed by chromatography (elution with H:E, 1:1), provided 578 mg (77%) of 4-bromo-1-methoxynaphthalene (**5**) [5467-58-3].

Bromination of 4 Using Conditions B. A reaction mixture containing 500 mg of **4** (3.20 mmol) was stirred at rt for 24 h using general procedure B. Standard ethereal workup and chromatography (elution with H:E, 1:1) provided 728 mg (97%) of bromide **5**.

Bromination of 4 Using Conditions C. A reaction mixture containing 500 mg of **4** (3.20 mmol) was stirred at rt for 72 h using general procedure C. Standard ethereal workup and chromatography (elution with H:E, 1:1) provided 675 mg (90%) of bromide **5**.

Bromination of 4 Using Conditions D. A reaction mixture containing 500 mg of **4** (3.20 mmol) was stirred at rt for 72 h using general procedure D. Standard ethereal workup, followed by chromatography (elution with H:E, 1:1), provided 638 mg (85%) of bromide **5**. Impurities arising from bromination at other positions were detected by ^{1}H NMR analysis (<5%).

Bromination of *o*-Methylanisole (6) Using Conditions A. A reaction mixture containing 500 mg of *o*-methylanisole (**6**) (4.09 mmol) was stirred at rt for 12 h using general procedure A. Standard ethereal workup and chromatography

(16) Others have recently independently reported the regiospecific bromination of benzene derivatives with DMSO−HBr. However, this report lacks detailed experimental procedures so as to allow the duplication of their results and presents an unlikely mechanism. See: Srivastava, S. K.; Chauhan, P. M. S.; Bhaduri, A. P. *J. Chem. Soc., Chem. Commun.* **1996**, 2679.

(elution with H:E, 5:1) provided 675 mg (82%) of 4-bromo-2-methylanisole (**7**) [578-58-5].

Bromination of 6 Using Conditions B. A reaction mixture containing 500 mg of **6** (4.09 mmol) was stirred at rt for 12 h using general procedure B. Standard ethereal workup and chromatography (elution with H:E, 5:1) provided 708 mg (86%) of bromide **7**.

Bromination of 6 Using Conditions C. A reaction mixture containing 500 mg of **6** (4.09 mmol) was stirred at rt for 5 min using general procedure C. Standard ethereal workup, followed by chromatography (elution with H:E, 5:1), provided 685 mg (75%) of bromide **7**.

Bromination of 6 Using Conditions D. A reaction mixture containing 500 mg of **6** (4.09 mmol) was stirred at rt for 2 h using general procedure D. Standard ethereal workup, followed by chromatography (elution with H:E, 5:1), provided 685 mg (75%) of bromide **7**.

Bromination of *m*-Methylanisole (8) Using Conditions A. A reaction mixture containing 500 mg of **8** (4.09 mmol) was stirred at rt for 12 h using general procedure A. Standard ethereal workup and chromatography (elution with H:E, 10:1) provided 749 mg (91%) of 4-bromo-3-methylanisole (**9**) [100-84-5].

Bromination of 8 Using Conditions B. A reaction mixture containing 500 mg of **8** (4.09 mmol) was stirred at rt for 12 h using general procedure B. Standard ethereal workup and chromatography (elution with H:E, 10:1) provided 745 mg (90%) of bromide **9**.

Bromination of 8 Using Conditions C. A reaction mixture containing 500 mg of **8** (4.09 mmol) was stirred at rt for 20 min using general procedure C. Standard ethereal workup and chromatography (elution with H:E, 10:1) provided 561 mg (68%) of bromide **9**. Continued elution afforded a complex mixture of polybrominated products that were not characterized.

Bromination of 8 Using Conditions D. A reaction mixture containing 500 mg of **8** (4.09 mmol) was stirred at rt for 20 min using general procedure D. Standard ethereal workup and chromatography (elution with H:E, 10:1) provided 734 mg (89%) of bromide **9**. Continued elution afforded a complex mixture of polybrominated products that were not characterized.

Bromination of *p*-Methylanisole (10) Using Conditions A. A reaction mixture containing 500 mg of *p*-methylanisole (**10**) (4.09 mmol) was stirred at rt for 72 h using general procedure A. Standard ethereal workup and chromatography (elution with H:E, 5:1) gave 634 mg (77%) of 2-bromo-4-methylanisole (**11**) [104-93-8].

Bromination of 10 Using Conditions B. A reaction mixture containing 500 mg of **10** (4.09 mmol) was stirred at rt for 72 h using general procedure B. Standard ethereal workup and chromatography (elution with H:E, 5:1) provided 617 mg (75%) of bromide **11**.

Bromination of 10 Using Conditions C. A reaction mixture containing 500 mg of **10** (4.09 mmol) was stirred at rt for 20 min using general procedure C. Standard ethereal workup and chromatography (elution with H:E, 5:1) provided 610 mg (74%) of bromide **11**.

Bromination of 10 Using Conditions D. A reaction mixture containing 500 mg of **10** (4.09 mmol) was stirred at rt for 5 min using general procedure D. Standard ethereal workup and chromatography (elution with H:E, 5:1) provided 792 mg (91%) of bromide **11**.

Bromination of *m*-Dimethoxybenzene (12) Using Conditions A for 5 Min. A reaction mixture containing 500 mg of **12** (3.62 mmol) was stirred at rt for 5 min using general procedure A. Standard ethereal workup and chromatography (elution with H:E, 10:1) provided 258 mg of unreacted starting material [H:E, 4:1, R_f **12** = 0.60]. Continued elution provided 265 mg (34%) of 1-bromo-2,4-dimethoxybenzene (**13**) [17715-69-4, H:E, 4:1, R_f **13** = 0.50].

Bromination of 12 Using Conditions A for 20 Min. A reaction mixture containing 500 mg of **12** (3.62 mmol) was stirred at rt for 20 min using general procedure A. Standard ethereal workup and chromatography (elution with H:E, 10:1) provided 933 mg (89%) of 4,6-dibromo-1,3-dimethoxybenzene (**14**) [24988-36-1, H:E, 4:1, R_f **14** = 0.21].

Bromination of 12 Using Conditions B for 5 Min. A reaction mixture containing 500 mg of **12** (3.62 mmol) was stirred at rt for 5 min using general procedure B. Standard workup and chromatography (elution with H:E, 10:1) provided 780 mg (73%) of dibromide **14**.

Bromination of 12 Using Conditions B for 20 Min. A reaction mixture containing 500 mg of **12** (3.62 mmol) was stirred at rt for 20 min using general procedure B. Standard workup and chromatography (elution with H:E, 10:1) provided 954 mg (87%) of dibromide **14**.

Bromination of 12 Using Conditions C. A reaction mixture containing 500 mg of **12** (3.62 mmol) was stirred at rt for 5 min using general procedure C. Standard workup and chromatography (elution with H:E, 10:1) provided 857 mg (80%) of dibromide **14**.

Bromination of 12 Using Conditions D. A reaction mixture containing 500 mg of **12** (3.62 mmol) was stirred at rt for 5 min using general procedure D. Standard workup, followed by chromatography (elution with H:E, 10:1), furnished 825 mg (77%) of dibromide **14**.

Bromination of 2-Isopropylphenol (15) Using Conditions A. To a stirred solution of 20.21 g (0.15 mol) of **15** in DMSO (150 mL, 2.11 mol) was added dropwise 100 mL of aqueous HBr (88 mmol of a 48% solution). Analysis by TLC indicated that the reaction was complete after a 24-h period at rt. Standard workup, followed by chromatography (elution with H:E, 4:1), gave 28.70 g (90%) of bromide **16** [26307-50-6].

Large-Scale Bromination of 15 Using Conditions B. To a stirred solution of 20.20 g (0.15 mol) of **15** in AcOH (200 mL) was added 100 mL of aqueous HBr (88 mmol of a 48% solution), followed by the dropwise addition of 100 mL of DMSO (1.40 mol). Analysis by TLC indicated that the reaction was complete after 5 min at rt. Standard ethereal workup, followed by chromatography (elution with H:E, 1:1), gave 29.05 g (91%) of bromide **16**.

Bromination of 15 Using Conditions C. A reaction mixture containing 500 mg of **15** (3.67 mmol) was stirred at rt for 5 min using general procedure C. Standard ethereal workup and chromatography (elution with H:E, 1:1), gave 173 mg (23%) of bromide **16** [H:E, 2:1, R_f **16** = 0.81]. Continued elution afforded 690 mg (64%) of 6-(1-methylethyl)-2,4-dibromophenol (**17**) [90562-17-7], (H:E, 4:1, R_f **17** = 0.45).

Bromination of 15 Using Conditions D. A reaction mixture containing 500 mg of **15** (3.67 mmol) was stirred for 5 min using general procedure D. Standard ethereal workup, followed by chromatography (elution with H:E, 1:1), gave 494 mg (63%) of dibromide **16** and 333 mg (31%) of dibromide **17**.

Bromination of *p*-Cresol (18) Using Conditions A. A reaction mixture containing 500 mg of *p*-cresol (4.63 mmol) was stirred at rt for 48 h using general procedure A. Standard workup, followed by chromatography (elution with H:E, 4:1), gave 763 mg (88%) of 2-bromo-4-methylphenol (**19**) [6627-55-0].

Bromination of 18 Using Conditions B. A reaction mixture containing 500 mg of *p*-cresol (4.63 mmol) was stirred at rt for 2 h using general procedure B. Standard workup and chromatography (elution with H:E, 4:1) provided 750 mg (87%) of bromide **19**.

Bromination of 18 Using Conditions C. A reaction mixture containing 500 mg of *p*-cresol (4.63 mmol) was stirred at rt for 30 min using general procedure C. Standard workup and chromatography (elution with H:E, 4:1) provided 756 mg (87%) of bromide **19** along with a trace amount of 2,6-dibromo-4-methylphenol (**20**) [2432-14-6].

Bromination of 18 Using Conditions D. A reaction mixture containing 500 mg of *p*-cresol (4.63 mmol) was stirred at rt for 30 min using general procedure C. Standard workup and chromatography (elution with H:E, 4:1) provided 761 mg (88%) of bromide **19** along with a trace amount of dibromide **20**.

Bromination of Vanillin (21) Using Conditions A. A reaction mixture containing 500 mg of vanillin (3.29 mmol) was stirred at rt for 12 h using general procedure A. Standard

workup and chromatography (elution with H:E, 5:2) provided 546 mg (72%) of 3-bromo-4-hydroxy-5-methoxybenzaldehyde (**22**) [2973-76-4].

Bromination of 21 Using Conditions B. A reaction mixture containing 500 mg of vanillin (3.29 mmol) was stirred at rt for 12 h using general procedure B. Standard workup, followed by chromatography (elution with H:E, 5:2), provided 433 mg (57%) of **22**.

Bromination of 21 Using Conditions C. A reaction mixture containing 500 mg of vanillin (3.29 mmol) was stirred at rt for 24 h using general procedure C. Standard ethereal workup, followed by chromatography (elution with H:E, 5:2), provided 192 mg of unreacted vanillin and 364 mg (48%) of bromide **22**.

Bromination of 21 Using Conditions D. A reaction mixture containing 500 mg of vanillin (3.29 mmol) was stirred at rt for 20 min using general procedure D. Standard ethereal workup, followed by chromatography (elution with H:E, 5:2), provided 759 mg (80%) of **22**.

Bromination of Aniline (23) Using Conditions A. A reaction mixture containing 500 mg (5.37 mmol) of aniline was stirred at rt for 6 h using general procedure A. The reaction mixture was diluted with water and made basic by the slow addition of solid NaOH. Standard ethereal workup, followed by chromatography (elution with H:E, 5:1), gave 705 mg (76%) of 4-bromoaniline (**24**) [106-40-1], which was homogeneous by TLC analysis [H:E, 1:2, R_f **23** = 0.55, R_f **24** = 0.70].

Bromination of 23 Using Conditions B. A reaction mixture containing 500 mg (5.37 mmol) of aniline was stirred at rt for 2 h using general procedure B. The reaction mixture was diluted with water and made basic by the slow addition of solid NaOH. Standard ethereal workup, followed by chromatography (elution with H:E, 5:1), gave 685 mg (74%) of bromide **24**. No further bromination resulted when the above conditions were maintained for a 6-h period.

Bromination of 23 Using Conditions C. A reaction mixture containing 500 mg (5.37 mmol) of aniline was stirred at rt for 5 min using general procedure C. The reaction mixture was diluted with water and made basic by the slow addition of solid NaOH. Standard ethereal workup and chromatography (H:E, 5:1) gave 179 mg (19%) of bromide **24**. Continued elution furnished 449 mg (33%) of 2,4-dibromobenzeneamine (**25**) [615-57-6] and 350 mg (30%) of 2,4,6-tribromobenzenamine (**26**) [147-82-0].

Bromination of 23 Using Conditions D. A reaction mixture containing 500 mg (5.37 mmol) of aniline was stirred at rt for 5 min using general procedure D. The reaction mixture was diluted with water and made basic by the slow addition of solid NaOH. Standard workup and chromatography (H:E, 5:1) gave 201 mg (21%) of bromide **24**. Continued elution furnished 549 mg (41%) of dibromide **25** and 361 mg (31%) of tribromide **26**.

Bromination of *N*,*N*-Dimethylaniline (27) Using Conditions A. A reaction mixture containing 500 mg (4.13 mmol) of **27** was stirred at rt for 24 h using general procedure A. The reaction mixture was diluted with water and made basic by the slow addition of solid NaOH. Standard workup and chromatography (H:E, 1:1) gave 356 mg of bromide **28** (43%) [586-77-6], which was homogenous by TLC analysis as well as unreacted **27**.

Bromination of 27 Using Conditions B. A reaction mixture containing 500 mg (4.13 mmol) of aniline **27** was stirred at rt for 24 h using general procedure B. The reaction mixture was diluted with water and made basic by the slow addition of solid NaOH. Standard workup, followed by chromatography (H:E, 1:1), gave 555 mg of a 1:1 mixture of **28** and unreacted **27**. On the basis of NMR analysis, this corresponds to a 42% yield of bromide **28**.

Bromination of 27 Using Conditions C. A reaction mixture containing 500 mg (4.13 mmol) of **27** was prepared using general procedure C and stirred at rt for 5 min. [Note: Solids formed on addition of the Br_2.] The reaction mixture was diluted with water and made basic by the slow addition of solid NaOH. Standard workup, followed by chromatography (H:E, 1:1), gave 498 mg of bromide **28** (60%).

Bromination of 27 Using Conditions D. A reaction mixture containing 500 mg (4.13 mmol) of **27** was prepared using general procedure D and stirred at rt for 5 min. The reaction mixture was diluted with water and made basic by the slow addition of solid NaOH. Standard workup and chromatography (H:E, 1:1) gave 560 mg (68%) of bromide **28** and 335 mg (29%) of 2,4-dibromo-*N*,*N*-dimethylbenzenamine (**29**) [64230-2-9].

Bromination of Veratrole (30) Using Conditions A. A reaction mixture containing 500 mg of veratrole (3.62 mmol) was stirred at rt for 24 h using general procedure A. Standard workup and chromatography (elution with H:E, 10:1) provided 688 mg (87%) of 4-bromoveratrole (**31**) [2859-78-1].

Bromination of 30 Using Conditions B. A reaction mixture containing 500 mg of veratrole (3.62 mmol) was stirred at rt for 24 h using general procedure B. Standard workup and chromatography (elution with H:E, 10:1) provided 566 mg (72%) of bromide **31**.

Bromination of 30 Using Conditions B at Reflux. A reaction mixture containing 500 mg of veratrole (3.62 mmol) was prepared using general procedure B and refluxed for 2 h. Standard workup and chromatography (elution with H:E, 10:1) provided 803 mg (75%) of 4,5-dibromo-1,2-dimethoxybenzene (**32**) [37875-73-1].

Bromination of 30 Using Conditions C. A reaction mixture containing 500 mg of veratrole (3.62 mmol) was prepared using general procedure C and was stirred at rt for 5 h. Standard workup provided 774 mg of a mixture of bromides **31** and **32**. On the basis of NMR analysis of this residue, bromide **31** was produced in 52% yield, while dibromide **32** was produced in 35% yield.

Bromination of 30 Using Conditions D. A reaction mixture containing 500 mg of veratrole (3.62 mmol) was prepared using general procedure D and was stirred at rt for 2 h. Standard workup and chromatography (elution with H:E, 10:1) provided 613 mg of a mixture of bromides **31** and **32**. On the basis of NMR analysis of this residue, bromide **31** was produced in 49% yield, while dibromide **32** was produced in 21% yield.

Bromination of 2-Isopropylphenol (15) Using Conditions B at Reflux. A reaction mixture containing 500 mg (3.67 mmol) of **15** was stirred at rt for 5 min using general procedure B. The mixture was then refluxed for a 2-h period. Standard ethereal workup, followed by chromatography (elution with H:E, 4:1), provided 860 mg (80%) of dibromide **17**.

Bromination of *p*-Cresol (18) Using Conditions B at Reflux. A reaction mixture containing 500 mg (4.63 mmol) of **18** was prepared using general procedure B except that the reaction mixture was refluxed for 2 h. Standard ethereal workup, followed by chromatography (elution with H:E, 4:1), provided 965 mg (99%) of dibromide **20**.

Bromination of *p*-Bromoaniline (24) Using Conditions B at Reflux. A reaction mixture containing 500 mg (2.90 mmol) of *p*-bromoaniline (**24**) was prepared using general procedure B and heated at reflux for 4 h. The reaction mixture was diluted with water and made basic by the slow addition of solid NaOH. Standard workup and chromatography (H:E, 5:1) gave 959 mg (82%) of tribromide **26**.

Preparation of 1-Chloro-2-methoxynaphthalene (34). To a stirred suspension of 500 mg (3.20 mmol) of **2** in AcOH (15 mL) was added 5 mL of aqueous HCl (61.0 mmol of a 37% solution) followed by the dropwise addition of 5 mL of DMSO (70.00 mmol). During this addition the substrate dissolved. The reaction mixture was stirred for 30 min at rt and then refluxed for 20 min. Standard ethereal workup, followed by chromatography (elution with H:E, 10:1 gradient elution to 2:1), gave 170 mg (28%) of chloride **34** [13101-92-3]. Continued elution gave a complex mixture of compounds.

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