Hypervalent Iodine Chemistry: Mechanistic Investigation of the Novel Haloacetoxylation, Halogenation, and Acetoxylation Reactions of 1,4-Dimethoxynaphthalenes

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Treatment of 1,4-dimethoxynaphthalenes with iodosobenzene diacetate and trimethylsilyl chloride or bromide furnished the haloacetoxylated, acetoxylated, and halogenated 1,4-dimethoxynaphthalenes in excellent yield. The reaction pathway for each transformation was shown to be a function of reagent stoichiometry. A mechanistic hypothesis is presented that rationalizes the reaction pathways and explains the subtle differences in the halogenation reactions. The acetoxylation, for example, is thought to involve the formation of an iodonium ion that promotes the nucleophilic addition of acetate ion and subsequent 1,2-acetyl migration. Bromination occurs as a direct result of the oxidation of trimethylsilyl bromide to bromine, followed by electrophilic aromatic substitution. Chlorination is thought to proceed *via* a radical process and *not* the formation of molecular chlorine from the dissociation of iodosobenzene dichloride. The haloacetoxylation reaction also appears to be fairly specific for 1,4-dimethoxynaphthalenes, since the analogous reaction with a 1,4-dimethoxybenzene derivative was unsuccessful.

Introduction

Hypervalent iodine reagents have become increasingly popular for affecting a variety of synthetic transformations.[1,2] This may be attributed to their ambiphilic nature which is a direct result of the ability to vary both the apical ligands on iodine and the electronic nature of the aryl group. This, in turn, allows the reactivity of the reagent to be varied to facilitate a particular transformation. In addition to these features, the iodoarene byproduct is relatively innocuous, avoiding the high toxicity of the more traditional lead- and selenium-based reagents. Furthermore, the iodoarene may be recovered, oxidized, and then resubmitted to the reaction, making the process relatively environmentally benign.

In a preliminary study, we described a series of complementary haloacetoxylation reactions with 1,4-dimethoxynaphthalenes using the reagent combination of iodosobenzene diacetate and trimethylsilyl bromide.[3] This reaction was a serendipitous discovery during the course of our synthetic studies aimed at the total synthesis of fredericamycin A,[4] in which the bromination of the ethylene ketal **1** to afford **3** was required (eq 1). Prior to these studies relatively few examples of the halogenation of aromatic systems using hypervalent iodine chemistry had been reported.[5] Kita and co-workers have, however, described the nucleophilic functionalization of electron rich aryl ethers with carbon, oxygen, nitrogen, and sulfur nucleophiles. The reactions were proposed to involve a radical cation species, formed between the electron rich aromatic substrate and iodosobenzene bis-(trifluoroacetate), that promoted nucleophilic aromatic substitution.[6] Herein, we provide a full account of our work, in which we propose alternative mechanistic hypotheses for the reactions of 1,4-dimethoxynaphthalenes with iodosobenzene diacetate and trimethylsilyl halides.

Results and Discussion

In the course of our synthetic studies, the regiospecific bromination of the ethylene ketal **1** was required. Attempted bromination with a standard electrophilic bromide source (NBS) failed to afford the desired bromide **3**, and thus we decided to examine alternative sources of bromide ion. Magnus *et al.* demonstrated that the combination of iodosobenzene and a trimethylsilyl halide provides an electrophilic halogen source ($PhIX_2$ where X = Cl and Br), which readily undergoes electrophilic reactions with silyl enol ethers.[7] Treatment of **1** with iodosobenzene diacetate and trimethylsilyl bromide furnished 3-acetoxy-2-bromo-1,4-dimethoxynaphthalene (**2**) in 57% yield, rather than the desired 2-bromo-3,3-(ethylenedioxy)-1,4-dimethoxynaphthalene (**3**) (eq 1). *This novel transformation may be envisioned as the formal addition of AcOBr to the benzyne derived from 1,4-dimethoxynaphthalene.* This reaction clearly deserved further investigation.

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

(1) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH: New York, 1992.

(2) (a) Varvoglis, A. *Synthesis* **1984**, 709. (b) Merkushev, E. B. *Rus. Chem. Rev.* **1987**, *56*, 826. (c) Moriarty, R. M.; Vaid, R. K.; Koser, G. F. *Synlett* **1990**, 365. (d) Moriarty, R. M.; Vaid, R. K. *Synthesis* **1990**, 431. (e) Stang, P. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 274. (f) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123.

(3) Evans, P. A.; Brandt, T. A. *Tetrahedron Lett.* **1996**, 37, 6443.

(4) Evans, P. A.; Brandt, T. A. *Tetrahedron Lett.* **1996**, 37, 1367.

(5) For related examples of halogenation of aromatic systems using hypervalent iodine reagents, see: Neu, R. *Ber. Dtsch. Chem. Ges.* **1939**, *72*, 1505. Ogata, Y.; Aoki, K. *J. Am. Chem. Soc.* **1968**, *90*, 6187. Angelini, G.; Sleiter, G. *Gazz. Chim. Ital.* **1975**, *105*, 961. Amey, R. L.; Martin, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 5294. Merkushev, E. B.; Simakhina, N. D.; Koveshnikova, G. M. *Synthesis* **1980**, 486. Gallos, J.; Varvoglis, A. *J. Chem. Res., Synop.* **1982**, 150. Robins, M. J.; Barr, P. J.; Giziewicz, J. *Can. J. Chem.* **1982**, *60*, 554. Bovonsombat, P.; Djuardi, E.; McNelis, E. *Tetrahedron Lett.* **1994**, *35*, 2841 and pertinent references cited therein.

(6) (a) Kita, Y.; Tohma, H.; Inagaki, M.; Hatanka, K.; Yakura, T. *Tetrahedron Lett.* **1991**, *32*, 4321. (b) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684. (c) Kita, Y.; Takada, T.; Mihara, S.; Tohma, H. *Synlett* **1995**, 211. (d) Kita, Y.; Takada, T.; Mihara, S.; Whelan, B. A.; Tohma, H. *J. Org. Chem.* **1995**, *60*, 7144.

(7) Magnus, P.; Lacour, J.; Evans, P. A.; Roe, M. B.; Hulme, C. *J. Am. Chem. Soc.* **1996**, *118*, 3406.

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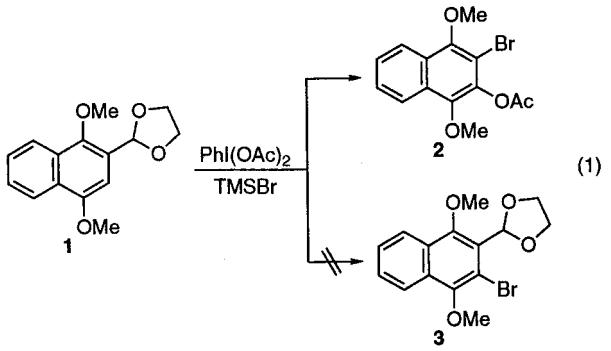
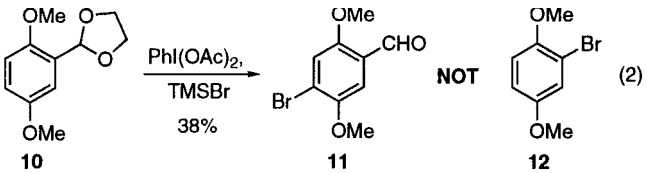


Table 1 summarizes the results from our detailed investigation of this novel chemistry. It is clear that the reagent stoichiometry governs the reaction pathway. This study also explored the scope and limitations of the haloacetoxylation, halogenation, and acetoxylation reactions of 1,4-dimethoxynaphthalenes with iodosobenzene diacetate and trimethylsilyl halides.

The optimum conditions for the *one-pot haloacetoxylation* of the ethylene ketal **1** and 1,4-dimethoxynaphthalene (**4**) required the sequential addition of iodosobenzene diacetate and trimethylsilyl bromide, followed by 2 equiv of iodosobenzene diacetate, to furnish 3-acetoxy-2-bromo-1,4-dimethoxynaphthalene (**2**) in good yield (entries 1 and 2). The 1,4-dimethoxynaphthalene (**4**), available from 1,4-naphthoquinone, provides a versatile intermediate for synthetic applications and demonstrates that the ethylene ketal is not essential for this reaction. Interestingly, the attempted chloroacetoxylation of **1** and **4** under similar conditions with trimethylsilyl chloride failed to afford **9**. Selective bromination of **1** and **4** was achieved by simply reducing the amount of iodosobenzene diacetate (entries 3 and 4), and chlorination of **4** was achieved using trimethylsilyl chloride (entry 5). The bromide **5** and chloride **6** could also be further brominated (entries 6 and 7), and in fact the dibromide **7** could be prepared directly from the parent 1,4-dimethoxynaphthalene (**4**) in a *one-pot* process (entry 8). The dibromide **7** provides a useful benzyne surrogate for target directed synthesis.[8] Interestingly, neither the bromide **5** or the chloride **6** chlorinated smoothly (see eqs 6 and 7). The selective acetoxylation of **5** and **6** was also examined, in which the corresponding haloacetoxylated adducts **2** and **9** were obtained in good yields (entries 9 and 10).

The attempted extension of this chemistry to electron rich benzene derivatives did not proceed as expected. Treatment of the ethylene ketal **10** under the standard brominating reaction conditions gave the bromo aldehyde **11** in 38% yield rather than the expected *ipso*-substitution product **12** (eq 2).



Mechanistic Hypothesis for Halogenation and Acetoxylation Reactions

(a) Halogenation. Kita and co-workers proposed that electron rich aryl ethers react with iodosobenzene bis(trifluoroacetate) to generate radical cations, which then promote nucleophilic substitution.[6] Therefore, in order to clarify the nature of the mechanism operative herein with iodosobenzene diacetate, a mechanistic study was undertaken. Preliminary analysis using UV spectroscopy did not provide any evidence to support the existence of a charge transfer complex between iodosobenzene diacetate or the iodosobenzene dihalide species with 1,4-dimethoxynaphthalene (**4**), as had been proposed for the more reactive iodosobenzene bis(trifluoroacetate).[6] Furthermore, the halogenation reactions occur in relatively nonpolar solvents (CH_2Cl_2), which is in sharp contrast to the substitutions reported with iodosobenzene bis(trifluoroacetate) which *require* polar protic solvents (CF_3CH_2OH).

An alternative mechanistic hypothesis put forward by Magnus and co-workers for silyl enol ethers proposes the formation of an iodosobenzene dihalide species as the electrophilic halogen source.[7] However, our results indicate that the chlorination and bromination reactions were distinct from one another, in terms of their relative rates of reaction and their substrate selectivity. The bromination of 1,4-dimethoxynaphthalene (**4**) is, for example, approximately 70 times faster than the analogous chlorination reaction. The two reactions also have contrasting specificity, as exemplified by their reaction with the ethylene ketal **1**. Bromination of **1** proceeds *via* an *ipso*-substitution[9] pathway to furnish the bromide

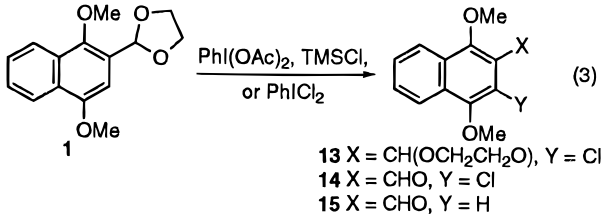
Table 1. Haloacetoxylation, Acetoxylation, and Halogenation of 1,4-Dimethoxynaphthalene Derivatives

entry	substrate R		rxn conds[a,b]	time	product Y	Z		yield (%)[c]
1		**1**	A	2 h	Br	OAc	**2**	75
2	H	**4**	A	50 min.	Br	OAc	**2**	80
3		**1**	B	30 min.	Br	H	**5**	99
4	H	**4**	B	30 min.	Br	H	**5**	99
5	H	**4**	C	6 h	Cl	H	**6**	83
6	Br	**5**	B	72 h	Br	Br	**7**	97
7	Cl	**6**	B	48 h	Cl	Br	**8**	97
8	H	**4**	D	50 h	Br	Br	**7**	94
9	Br	**5**	E	2 h	Br	OAc	**2**	76
10	Cl	**6**	E	2 h	Cl	OAc	**9**	71

[a] Reactions were all run using 1 mmol of the 1,4-dimethoxynaphthalene. [b] Method A: (i) $PhI(OAc)_2$, TMSBr, 0 °C, (ii) $PhI(OAc)_2$, 0 °C to rt. Method B: $PhI(OAc)_2$, TMSBr, 0 °C. Method C: $PhI(OAc)_2$, TMSCl, 0 °C to rt. Method D: (i) $PhI(OAc)_2$, TMSBr, 0 °C to rt, (ii) $PhI(OAc)_2$, TMSBr 0 °C to rt. Method E: $PhI(OAc)_2$, cat. TMSBr, 0 °C to rt. [c] Isolated yields.

(8) Giles, R. G. F.; Hughes, A. B.; Sargent, M. V. *J. Chem Soc., Perkin Trans. 1* **1991**, 1581.

5, while the chlorination under analogous conditions afforded a mixture of **13**, **14**, and **15** (eq 3). *This evidence clearly suggests that the two reactions do not proceed via the same mechanistic pathway.*



NMR and UV−vis experiments confirm that iodosobenzene diacetate and trimethylsilyl bromide produce bromine. Figure 1 depicts a series of NMR spectra that show the clean and rapid (*ca*. 5 min) reduction of iodosobenzene diacetate to iodobenzene in the absence of the substrate, (Figure 1, A and B), which upon addition of **4** results in conversion to **5** in *ca*. 5 min (Figure 1, C). Figure 2 provides a UV−vis absorbance trace illustrating rate of consumption of bromine upon addition of the 1,4-dimethoxynaphthalene (**4**).[10,11] Treatment of **4** or the ethylene ketal **1** with bromine also furnished the bromide **5** in excellent yield, confirming this assumption. Hence, iodosobenzene diacetate/trimethylsilyl bromide provides a convenient source of molecular bromine.

In order to gain further insight into the chlorination reactions, a similar series of NMR experiments were carried out to determine the nature of the chlorinating species, as illustrated in Figure 3. Treatment of iodosobenzene diacetate with trimethylsilyl chloride leads to a mixture of iodosobenzene dichloride and what

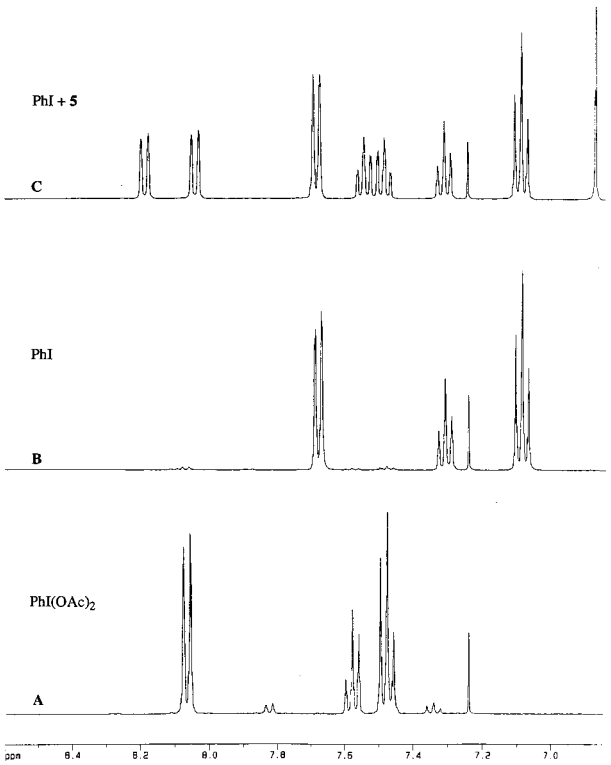


Figure 1. A = $PhI(OAc)_2$; B = $PhI(OAc)_2$/TMSBr affords PhI and Br_2 after 5 min; C = $PhI(OAc)_2$/TMSBr and **4** furnishes PhI and **5** after 5 min.

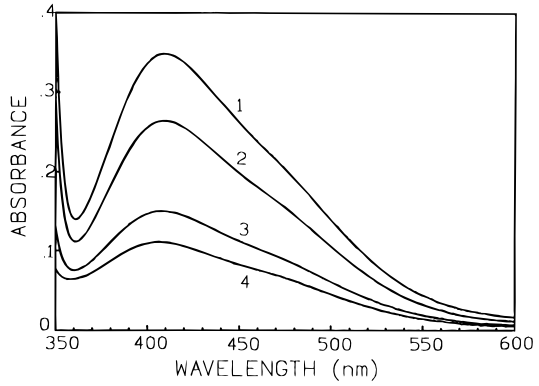
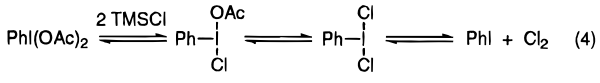
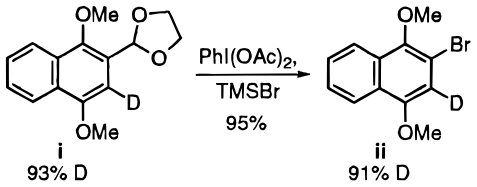


Figure 2. Plot of the UV−vis absorbance of Br_2 (from $PhI(OAc)_2$, TMSBr) as a function of time upon addition of 1,4-dimethoxynaphthalene (**4**): 1 = 10 s, 2 = 60 s, 3 = 290 s, 4 = 1200 s.

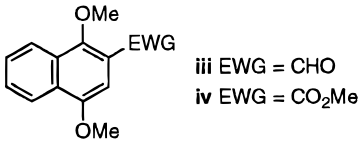
appears to be the mixed iodosobenzene chloroacetate species (Figure 3, B, and eq 4). Addition of the 1,4-dimethoxynaphthalene (**4**) gave the chloride **6** (Figure 3, D). The reaction is considerably slower than the analogous bromination reaction, and iodobenzene is formed as the reaction proceeds over *ca*. 6 h compared to 5 min (compare Figure 1, C, to Figure 3, C). Furthermore, there is only a trace amount of iodobenzene present in the NMR spectrum until the addition of the substrate. Iodosobenzene dichloride has been shown to dissociate to iodobenzene and chlorine (eq 4), and the dissociation constant is considerably lower in nonpolar solvents.[12] Therefore, it was entirely possible that the chlorinations described herein could be the result of a slow dissociation to form chlorine.



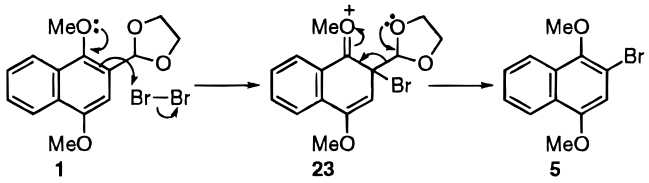
(9) The regioselectivity and substrate specificity were examined in order to confirm our assumptions with respect to the *ipso*-substitution of the ethylene acetal **1**. Treatment of the deuterated ethylene ketal **i** (93% D incorporation) under the standard brominating conditions gave the bromide **ii** (91% D incorporation) in 95% yield, confirming the regiochemistry.



This reaction appears to be specific for the ethylene ketal, since the attempted bromination of the aldehyde **iii** and the ester **iv** did not afford the *ipso*-substitution product **5**.



On the basis of these observations, it appears that the acetal facilitates the *ipso*-substitution through the formation of the an oxonium ion, as outlined in the proposed mechanism depicted below.



(10) The reducing power of the halide ions increases in the order $I^- > Br^- > Cl^- > F^-$; Gusarsky, E.; Treinin, A. *J. Phys. Chem.* **1965**, *69*, 3176. Trimethylsilyl iodide is readily oxidized to iodine with iodosobenzene diacetate. Treatment of the 1,4-dimethoxynaphthalene (**4**) with this reagent combination gave none of the desired iodide.

(11) The λ_{max} for the UV−vis absorbance for molecular bromine in dichloromethane was confirmed independently.

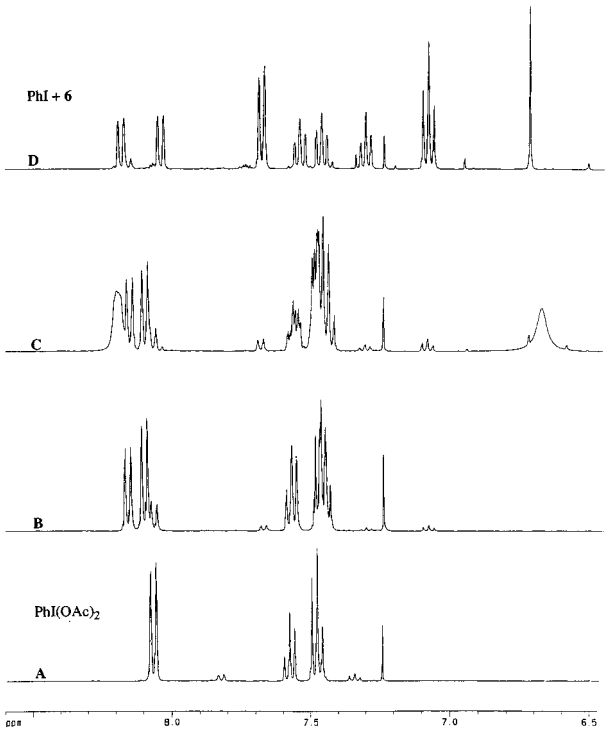
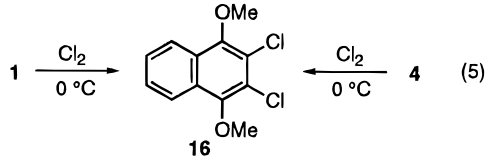


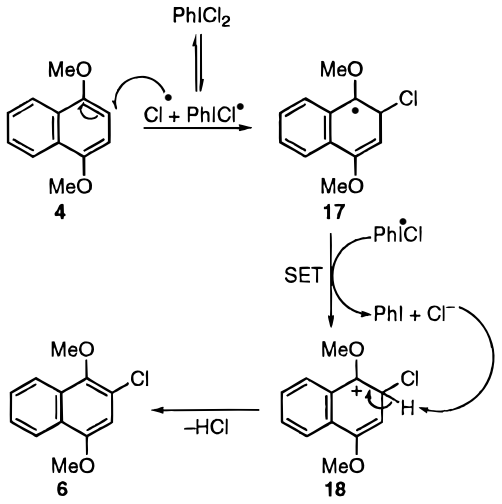
Figure 3. A = $PhI(OAc)_2$; B = $PhI(OAc)_2$/TMSCl leads to a ~1:1 mixture of PhIOAcCl/$PhICl_2$ after 1.5 h; C = $PhI(OAc)_2$/TMSCl and **4** furnishes a mixture containing PhI and **6** after 5 min; D = $PhI(OAc)_2$/TMSCl and **4** affords PhI and **6** after 6 h.

In order to test this hypothesis, the ethylene ketal **1** and the 1,4-dimethoxynaphthalene (**4**) were independently treated with molecular chlorine, which resulted in the rapid formation of 2,3-dichloro-1,4-dimethoxynaphthalene, in *ca.* 2 min, in addition to polychlorinated products (eq 5). The increased rate of reaction and poor selectivity are in complete contrast to the reagent derived from iodosobenzene diacetate and trimethylsilyl chloride. Furthermore, the *ipso*-substitution pathway of ethylene ketal **1** is not operative (see, eq 7) with the hypervalent iodine derived reagent and thus provides clear evidence for an alternative mechanistic pathway clearly demonstrating that chlorine is not the reagent responsible for the chlorination reactions.

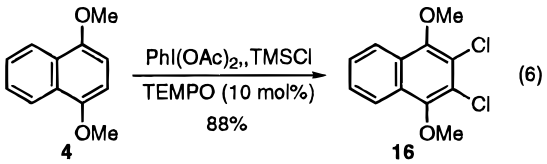


It was also possible that iodosobenzene dichloride was the reagent responsible for the chlorinations. To test this hypothesis an authentic sample was prepared from iodosobenzene and trimethylsilyl chloride.[7] Treatment of **4** with iodosobenzene dichloride nearly doubled the rate of reaction (3.5 h) and furnished the chloride **6** in 92% yield. Further insight into the possible reactive species was gained from the following experiments. Addition of a catalytic amount of the stable free radical TEMPO[13] (10 mol %) to the reaction, with the reagent

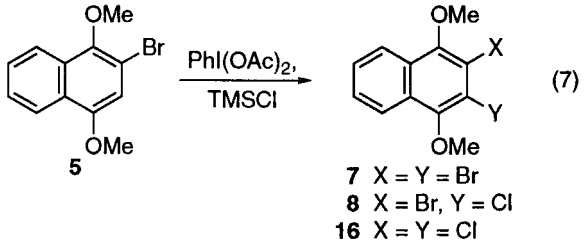
Scheme 1



prepared *in situ*, resulted in the clean and rapid conversion of **4** to **6** (98%) in *ca.* 30 min. Alternatively, photolysis of **4** with a sunlamp, with *in situ* formation of the reagent, furnished **6** (88%) in *ca.* 3.5 h. However, increasing the amount of TEMPO (10 equiv) retarded the rate of reaction significantly, with the reaction only 75% complete after *ca.* 48 h. Indeed, the catalytic role of the TEMPO is clearly demonstrated in the chlorination of **4** (eq 6), in which the dichloride **16** was obtained in *ca.* 2 h. The analogous transformation in the absence of TEMPO fails to go to completion even after *ca.* 48 h, affording a mixture of mono- and dichlorinated products.



The last piece of evidence to support the existence of a radical chlorination process was obtained from the attempted chlorination of the bromide **5**, in which scrambling of the halogens was observed (eq 7).



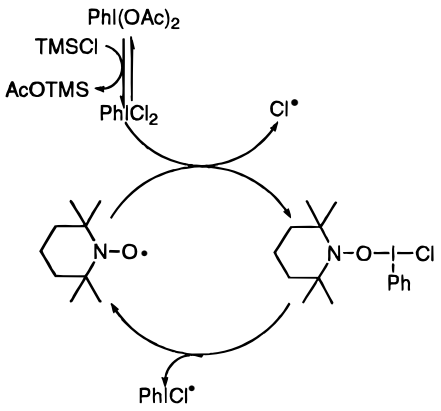
GC Ratio **7** : **8** : **16** = 16 : 60 : 24

Therefore, the chlorination presumably involves a radical process rather than an electrophilic pathway involving chlorine as outlined in Scheme 1. Homolysis of iodosobenzene diacetate can presumably provide a chlorine radical which then adds to the 1,4-dimethoxynaphthalene (**4**) to furnish **17**. The radical intermediate then undergoes a single electron transfer to afford **18**, iodobenzene, and chloride ion. The chloride ion then facilitates rearomatization to afford the chlorinated 1,4-dimethoxynaphthalene **6** and hydrogen chloride.

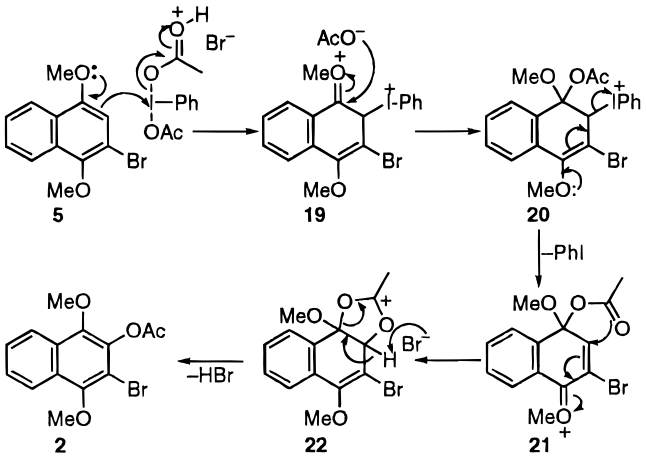
(12) (a) Keefer, R. M.; Andrews, L. J. *J. Am. Chem. Soc.* **1956**, *78*, 5350. (b) McCusker, P. A.; Makowski, H. S. *J. Am. Chem. Soc.* **1957**, *79*, 5185. (c) Jeffrey, E. A.; Andrews, L. J.; Keefer, R. M. *J. Org. Chem.* **1965**, *30*, 617. (d) Olah, G. A.; Piteau, M.; Laali, K.; Rao, C. B.; Farooq, O. *J. Org. Chem.* **1990**, *55*, 46.

(13) For an example of TEMPO as a radical trap in hypervalent iodine chemistry, see: Togo, H.; Aoki, M.; Kuramochi, T.; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2417.

Scheme 2

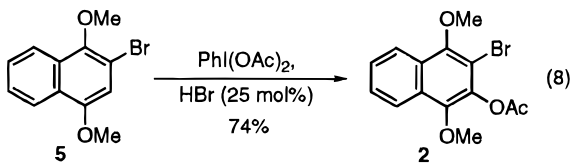


Scheme 3



The proposed catalytic role of TEMPO is outlined in Scheme 2. TEMPO can accelerate the initial rate of homolysis of iodosobenzene dichloride and the formation of a chloride radical. The hypervalent iodine/TEMPO adduct can then undergo further homolysis to regenerate the TEMPO which recatalyzes the initial homolysis. The hypervalent iodine radical that is formed is then likely to undergo single electron transfer. Although the exact mechanistic pathway is not known, this working hypothesis is consistent with the experimental results.

(b) Acetoxylation. The nature of the acetoxylation reaction was clarified from the following results. Preliminary studies demonstrated that the acetoxylation occurred with iodosobenzene diacetate and catalytic trimethylsilyl bromide. This combination had been demonstrated to furnish molecular bromine; hence it was unlikely that the trimethylsilyl bromide was directly responsible. The byproduct from the halogenation is hydrogen bromide. Indeed, treatment of the bromide **5** with iodosobenzene diacetate and a catalytic amount of hydrogen bromide furnished the acetoxylated bromide **2** in 74% yield (eq 8).



Therefore, the proposed mechanism for acetoxylation is outlined in Scheme 3. The formation of the iodonium ion **19** facilitates the 1,2-addition of the acetate ion to the oxonium ion. β-Elimination of the iodonium ion would give an ene-oxonium ion species **21** which could facilitate the acetyl migration. Rearomatization of the carbocation intermediate **22** would then give the acetoxylated bromide **2**.[14] This is in complete contrast to the more general reaction pathway in which 1,2- rather than 1,4-addition predominates and also explains the observed regiochemistry.[15]

In conclusion, we have developed a novel method for the haloacetoxylation, acetoxylation, and halogenation, of 1,4-dimethoxynaphthalenes using hypervalent iodine chemistry. A mechanistic hypothesis is forwarded that provides a plausible explanation for the difference in the halogenation reactions, based on oxidation potentials of the halide source, and the reason for the required stoichiometry ($PhI(OAc)_2$/TMSX) to effect both the halogenation and acetoxylation reactions. Interestingly, the haloacetoxylation reaction may be envisioned as the formal addition of AcOX to a benzyne, and it appears to be specific for 1,4-dimethoxynaphthalene derivatives. Although, the bromination reaction provides no real advantage over molecular bromine, the ability to selectively chlorinate with the hypervalent iodine reagent is likely to have numerous synthetic applications in light of our mechanistic findings.

Experimental Section

General. The chemical shifts of the ^{1}H NMR and ^{13}C NMR spectra were all recorded relative to chloroform or benzene. Multiplicity's were determined with the aid of a APT sequence, separating methylene and quaternary carbons = e (even) from methyl and methine = o (odd). Melting points are uncorrected. GLC analysis was carried out using an HP 6890 Series GLC system using an HP-1 (cross-linked methylsiloxane) capillary column (flow rate: 1 mL/min). UV experiments were performed on a Hewlett-Packard HP8452A diode-array spectrophotometer. All compounds were purified as specified and gave spectroscopic data consistent with being ≥95% the assigned structure. Analytical TLC was carried out on precoated 0.2 mm thick Merck 60 F_{254} silica plates. Flash chromatography was carried out using Merck silica gel 60 (230−400 mesh).

All reagents and starting materials were obtained from commercial suppliers (Acros, Aldrich, Fluka, and Lancaster) and were used without purification except where indicated. Dichloromethane was dried over and freshly distilled from calcium hydride. All reactions were carried out under an inert atmosphere of dry nitrogen using oven-dried or flame-dried glassware.

3-Acetoxy-2-bromo-1,4-dimethoxynaphthalene (2). Method A. Iodosobenzene diacetate (0.361 g, 1.12 mmol) was dissolved in anhydrous dichloromethane (6 mL) and cooled with stirring to 0 °C. Neat trimethylsilyl bromide (300 μL, 2.25 mmol) was added, and the mixture stirred at 0 °C for 30 min, resulting in a clear orange solution. 1,4-Dimethoxynaphthalene-2-carboxaldehyde ethylene ketal (**1**) (0.263 g, 1.01 mmol) was dissolved in anhydrous dichloromethane (2 mL) and added *via* a Teflon cannula. The reaction mixture was stirred for 1 h at 0 °C, resulting in the complete conversion of **1** to **5** (TLC control; 1:4 ethyl acetate/hexane). Additional iodosobenzene diacetate (0.652 g, 2.02 mmol) was then added in one portion, and the reaction mixture was stirred for a further hour at 0 °C. The reaction mixture was then warmed

(14) For an example of a similar mechanism for the acetoxylation of *p*-substituted acetanilides, see: Kokil, P. B.; Patil, S. D.; Ravindranathan, T.; Madhavan Nair, P. *Tetrahedron Lett.* **1979**, 989.

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to room temperature and partitioned between saturated aqueous $NaHCO_3$ solution and dichloromethane. The organic layers were combined, dried (Na_2SO_4), and filtered, and the solvent was removed *in vacuo* to afford the crude product. Purification by flash chromatography on silica gel (eluting with 1:9 ethyl acetate/hexane) furnished the *title compound* **2** (0.248 g, 75%) as an off-white crystalline solid.

Method B. 2-Bromo-1,4-dimethoxynaphthalene (**5**) (0.27 g, 1.01 mmol) was dissolved in anhydrous dichloromethane (10 mL) and cooled with stirring to 0 °C. Iodosobenzene diacetate (0.724 g, 2.25 mmol) was added to the solution followed by addition of neat trimethylsilyl bromide (34 μl, 0.25 mmol). The reaction mixture was stirred at 0 °C for an hour before being allowed to warm to room temperature where it was stirred for an additional hour. The reaction mixture was partitioned between saturated aqueous $Na_2S_2O_4$ solution and dichloromethane. The organic layers were combined, dried (Na_2SO_4), and filtered, and the solvent wars emoved *in vacuo* to afford the crude product. Purification by flash chromatography on silica gel (eluting with 1:9 ethyl acetate/hexane) furnished the *title compound* **2** (0.250 g, 76%) as an off-white crystalline solid.

Method C. Iodosobenzene diacetate (0.361 g, 1.11 mmol) was dissolved in anhydrous dichloromethane (6 mL) and cooled with stirring to 0 °C. Neat trimethylsilyl bromide (300 μL, 2.25 mmol) was added, and the mixture was stirred at 0 °C for 30 min, resulting in a clear orange solution. 1,4-Dimethoxynaphthalene (**4**) (0.191 g, 1.01 mmol) was dissolved in anhydrous dichloromethane (2 mL) and added *via* Teflon cannula. The reaction mixture was stirred for 40 min at 0 °C, resulting in the complete conversion of **4** to **5** by thin layer chromatography (1:4 ethyl acetate/hexane). Additional iodosobenzene diacetate (0.722 g, 2.22 mmol) was then added to the reaction in one portion. The reaction mixture was stirred for 10 min at 0 °C and then partitioned between a saturated aqueous $Na_2S_2O_4$ solution and dichloromethane. The organic layers were combined, dried (Na_2SO_4), and filtered, and the solvent was removed *in vacuo* to afford the crude product. Purification by flash chromatography on silica gel (eluting with 1:9 ethyl acetate/hexane) furnished the *title compound* **2** (0.266 g, 80%) as an off-white crystalline solid: mp 130−131 °C; IR ($CHCl_3$) 1776 (s), 1584 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.06−8.13 (m, 2H), 7.50−7.59 (m, 2H), 3.98 (s, 3H), 3.94 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$, APT) δ 168.28 (e), 150.69 (e), 144.69 (e), 137.70 (e), 128.05 (e), 127.36 (e), 127.03 (o), 126.86 (o), 122.54 (o), 122.39 (o), 109.49 (e), 62.04 (o), 61.66 (o), 20.65 (o); HRMS (M^+) calcd for $C_{14}H_{13}O_2{}^{80}Br$ 323.9997, found 323.9993.

2-Chloro-1,4-dimethoxynaphthalene (6). Iodosobenzene diacetate (0.395 g, 1.22 mmol) was dissolved in anhydrous dichloromethane (6 mL) and the opaque solution cooled to 0 °C with stirring. Neat trimethylsilyl chloride (212 μL, 2.45 mmol, freshly distilled from CaH_2) was added, and the mixture was stirred at 0 °C for 1 h, resulting in a slightly yellow solution. 1,4-Dimethoxynaphthalene (**4**) (0.209 g, 1.10 mmol) was dissolved in dichloromethane (2 mL) and then added *via* Teflon cannula, resulting in a more intense yellow color. The reaction mixture was stirred for 1 h at 0 °C and then warmed to room temperature and stirred for 5 h. The solvent was then removed *in vacuo* to afford the crude product. Purification by flash chromatography on silica gel (eluting with 1:49 and then 1:19 ethyl acetate/hexane) furnished the title compound **6**[16] (0.205 g, 83%) as a white crystalline solid: mp 76−80 °C; IR ($CHCl_3$) 3013 (m), 2939 (m), 1622 (m), 1582 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.18−8.22 (m, 1H), 8.04−8.08 (m, 1H), 7.44−7.59 (m, 2H), 6.74 (s, 1H), 3.96 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$, APT) δ 152.15 (e), 145.36 (e), 129.05 (e), 127.31 (o),125.60 (o), 125.30 (e), 122.50 (e), 122.42 (o), 121.61 (o), 105.50 (o), 61.26 (o), 55.76 (o); HRMS (M^+) calcd for $C_{12}H_{11}O_2Cl$ 222.0447, found 222.0458.

3-Acetoxy-2-chloro-1,4-dimethoxynaphthalene (9). 2-Chloro-1,4-dimethoxynaphthalene (**6**) (0.226 g, 1.02 mmol) was dissolved in anhydrous dichloromethane (10 mL) and cooled with stirring to 0 °C. Iodosobenzene diacetate (0.654 g, 2.25 mmol) was added to the solution followed by addition of neat trimethylsilyl bromide (34 μL, 0.25 mmol). The reaction mixture was stirred at 0 °C for an hour before being allowed to warm to room temperature where it was stirred for an additional hour. The reaction mixture was partitioned between a saturated aqueous $NaHCO_3$ solution and dichloromethane. The organic layers were combined, dried (Na_2SO_4), and filtered, and the solvent was removed *in vacuo* to afford the crude product. Purification by flash chromatography on silica gel (eluting with 1:9 ethyl acetate/hexane) furnished the *title compound* **9** (0.202 g, 71%) as an off-white crystalline solid: mp 119−124 °C; IR ($CHCl_3$) 1778 (s), 1589 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.06−8.11 (m, 2H), 7.50−7.56 (m, 2H), 3.99 (s, 3H), 3.94 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$, APT) δ 168.29 (e), 149.20 (e), 144.64 (e), 136.82 (e), 127.39 (e), 127.18 (e), 126.88 (o), 126.84 (o), 122.37 (o), 122.16 (o), 118.72 (e), 62.00 (o), 61.58 (o), 20.45 (o); HRMS (M^+) calcd for $C_{14}H_{13}O_4Cl$ 280.0502, found 280.0506.

2,3-Dichloro-1,4-dimethoxynaphthalene (16). Trimethylsilyl chloride (195 μL, 2.21 mmol) was added to a solution of iodosobenzene diacetate (0.363 g, 1.11 mmol) in anhydrous dichloromethane (5 mL) at 0 °C and stirred for *ca.* 1 h. 1,4-Dimethoxynaphthalene (**4**) (0.195 g, 1.04 mmol) and TEMPO (0.016 g, 10 mol %) were dissolved in anhydrous dichloromethane (2 mL) and then added *via* Teflon cannula to the reaction mixture. The reaction mixture was stirred for 1 h at 0 °C (TLC control for **4** to **6**; 1:4 ethyl acetate/hexanes). Trimethylsilyl chloride (198 μL, 2.24 mmol) was then added to a second portion of iodosobenzene diacetate (0.369 g, 1.12 mmol) in anhydrous dichloromethane (5 mL) at 0 °C and stirred for *ca.* 1 h. The solution of **6** was then added *via* Teflon cannula to this solution at 0 °C and the reaction warmed to room temperature and stirred for *ca.* 1 h. The reaction mixture was then concentrated *in vacuo* to afford a crude product which was purified by flash chromatography on silica gel (eluting with 1:39 then 1:19 ethyl acetate/hexane) to furnish the title compound **16**[17] (0.226 g, 88%) as an off-white crystalline solid: mp 105−107 °C; IR ($CHCl_3$) 2937 (w), 1563 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.04−8.12 (m, 2H),7.52−7.59 (m, 2H), 3.98 (s, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$, APT) δ 149.65 (e), 127.58 (e), 127.22 (o), 122.94 (e), 122.29 (o), 61.39 (o); HRMS (M^+) calcd for $C_{12}H_{10}O_2Cl_2$ 256.0057, found 256.0074.

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Supporting Information Available: Experimental details for the preparation and full characterization of **1**, **4**−**5**, **7**−**8**, **16**, and **ii**, in addition to ^1H-NMR spectra for compounds **1**−**2**, **4**−**9**, **16**, and **ii** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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