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Novel Haloacetoxylation of 1,4-Dimethoxynaphthalenes using Hypervalent Iodine Chemistry

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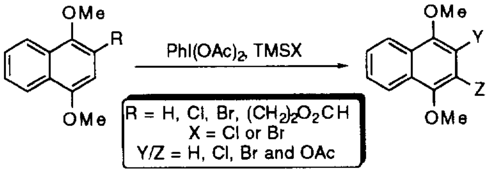
Abstract: *Treatment of 1,4-dimethoxynaphthalenes with iodosobenzene and trimethylsilyl chloride or bromide furnished the corresponding 2,3-haloacetoxylated-1,4-dimethoxynaphthalenes.*

Hypervalent iodine reagents have become extremely popular for effecting a variety of organic reactions.[1,2] This is due, in part, 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. The character of the reagent can thus, in principle, be fine-tuned to obtain the desired level of reactivity for a particular transformation. Recent reports on the nucleophilic functionalization of electron rich aryl ethers with carbon, oxygen, nitrogen and sulfur nucleophiles,[3] prompted the publication of our results on a series of complementary halogenation and oxygenation reactions.[4,5] In this paper, we describe the novel haloacetoxylation of a series of 1,4-dimethoxynaphthalenes (**Scheme 1**) with the reagent combination of iodosobenzene diacetate and trimethylsilyl bromide or chloride.

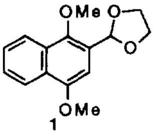
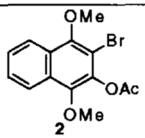
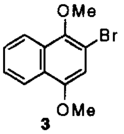
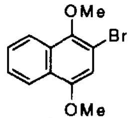
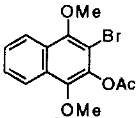
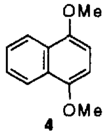
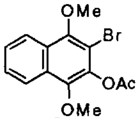
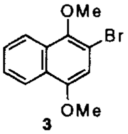
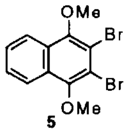
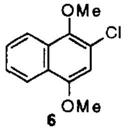
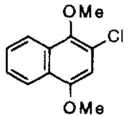
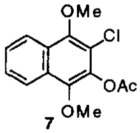
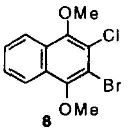
Scheme 1



In the course of our synthetic studies the bromination of the ethylene ketal **1** was required. Treatment of **1** with the reagent derived from iodosobenzene diacetate and trimethylsilyl bromide afforded 3-acetoxy-2-bromo-1,4-dimethoxynaphthalene **2** in 57% yield. *This transformation represents the formal addition of AcOBr to a benzyne.* **Table 1** summarizes the results of our investigation of this novel and potentially useful chemistry.

In order to further evaluate the merit of this novel reaction, and thus determine which reaction was responsible for the ipso-substitution of the ethylene ketal **1**, the stoichiometry of the reagent was modified. Treatment of **1** with iodosobenzene diacetate and trimethylsilyl bromide followed by an additional amount of iodosobenzene diacetate afforded 3-acetoxy-2-bromo-1,4-dimethoxynaphthalene

Table 1: Halogenation and Acetoxylation of 1,4-Dimethoxynaphthalene Derivatives

entry	1,4-dimethoxy-naphthalenes	reaction conditions[a]	time	product	yield (%)[b]
1	 1	PhI(OAc)$_2$ (1.1 eq), TMSBr (2.2 eq), then PhI(OAc)$_2$ (1.1 eq) 0 °C to RT	2 hrs	 2	75
2	"	PhI(OAc)$_2$ (1.1 eq), TMSBr (2.2 eq), 0 °C	30 min.	 3	99
3	 3	PhI(OAc)$_2$ (2.2 eq), TMSBr (0.25 eq), 0 °C to RT	2 hrs	 2	76
4	 4	PhI(OAc)$_2$ (1.1 eq), TMSBr (2.2 eq), 0 °C; then PhI(OAc)$_2$ (2 eq)	50 min.	 2	80
5	"	PhI(OAc)$_2$ (1.05 eq), TMSBr (2.1 eq), 0 °C	30 min.	 3	99
6	"	PhI(OAc)$_2$ (1.1 eq), TMSBr (2.2 eq), 0 °C to RT; then PhI(OAc)$_2$ (1.1 eq), TMSBr (2.2 eq), RT	2 days	 5	94
7	"	PhI(OAc)$_2$ (1.1 eq), TMSCl (2.2 eq), 0 °C to RT	22 hrs	 6	83
8	 6	PhI(OAc)$_2$ (2.0 eq), TMSBr (0.25 eq), 0 °C to RT	2 hrs	 7	71
9	"	PhI(OAc)$_2$ (1.25 eq), TMSBr (2.5 eq),0 °C to RT	48 hrs	 8	97

[a] Reactions were all carried out on a 1 mmol reaction scale.[6] [b] Isolated yields.[7]

2 in an improved 75% yield (**Table 1**, Entry 1). The product of the reaction could then be changed by simply reducing the amount of iodosobenzene diacetate, which resulted in the exclusive substitution of the ethylene ketal **1** to furnish the bromide **3** in near quantitative yield (Entry 2). This result implies that acetoxylation occurs subsequent to the bromination. In order to verify this assumption, the acetoxylation of the ethylene ketal **1** and the bromide **3** were examined. Attempted acetoxylation of the ethylene ketal **1** gave mainly recovered starting material. However, treatment of **3** with iodosobenzene diacetate followed by a catalytic amount of trimethylsilyl bromide afforded 3-acetoxy-2-bromo-1,4-dimethoxynaphthalene **2** in 76% yield (Entry 3), thus confirming the order of substitution.[8]

Despite the inherent novelty of the chemistry, the direct functionalization of the parent 1,4-dimethoxynaphthalene **4** would be more appealing for synthetic applications. Indeed, treatment of **4** with iodosobenzene diacetate and trimethylsilyl bromide followed by an additional amount of iodosobenzene diacetate afforded 3-acetoxy-2-bromo-1,4-dimethoxynaphthalene **2** in 80% yield (Entry 4). The 1,4-dimethoxynaphthalene **4** could also be mono-brominated in excellent yield (Entry 5), or converted to the dibromide **5** *via* the sequential addition of iodosobenzene diacetate and trimethylsilyl bromide in 94% overall yield for the one-pot process (Entry 6). Chlorination of the 1,4-dimethoxynaphthalene **4** was achieved by simply employing trimethylsilyl chloride, which resulted in the chloride **6** in 83% yield (Entry 7).[9] This intermediate could then be acetoxylated under similar conditions to those employed for the bromide **3** (Entry 3). Treatment of the chloride **6** with iodosobenzene diacetate followed by a catalytic amount of trimethylsilyl bromide furnished 3-acetoxy-2-chloro-1,4-dimethoxynaphthalene **7** in 71% yield (Entry 8). Interestingly, the direct chloroacetoxylation of the ethylene ketal **1** to **7** was unsuccessful. The chloride **6** was also brominated, to furnish 2-bromo-3-chloro-1,4-dimethoxynaphthalene **8** in excellent yield (Entry 9).

In conclusion, we have developed a novel method for the haloacetoxylation of 1,4-dimethoxynaphthalenes using hypervalent iodine chemistry. This transformation represents the formal addition of AcOX to a benzyne, and thus the 1,4-dimethoxynaphthalenes represent benzyne equivalents. The scope and proposed mechanisms by which these novel transformations are thought to proceed will be reported in a full account of this work.

Acknowledgments

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5. For an example of a similar acetoxylation reaction of *p*-substituted acetanilides, see Kokil, P. B.; Patil, S. D.; Ravindranathan, T.; Madhavan Nair, P. *Tetrahedron Lett.* **1979**, 989.

6. *Haloacetoxylation Procedure*: Iodosobenzene diacetate (0.361 g, 1.11 mmol) was dissolved in anhydrous dichloromethane (6 ml) and cooled with stirring to 0 °C. Trimethylsilyl bromide (300 μl, 2.25 mmol) was added neat and the mixture stirred at 0 °C for 30 minutes 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 minutes at 0 °C resulting in the complete conversion of **4** to **3** (TLC control; 1 : 4 ethyl acetate/hexane). Additional iodosobenzene diacetate (0.722 g, 2.22 mmol) was then added in one portion to the reaction. The mixture was stirred for 10 minutes at 0 °C then poured into saturated $Na_2S_2O_4$ solution (10 ml) and extracted with dichloromethane (3 x 10 ml). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered and concentrated *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 ($CHCl_3$) 3012 (w), 2938 (w), 2849 (w), 1776 (s), 1584 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.06-8.13 (2H, m), 7.50-7.59 (2H, m), 3.98 (3H, s) 3.94 (3H, s), 2.44 (3H, s); ^{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 (EI) calcd for $C_{14}H_{13}O_2{}^{80}Br$ 323.9997 found 323.9993

7. All new compounds exhibited spectroscopic (IR, ^1H and ^{13}C NMR) and analytical (HRMS) data in accord with the assigned structure.

8. The initial bromination step generates catalytic HBr, which has been *shown* to catalyze the acetoxylation reaction.[10]

9. Trimethylsilyl iodide is readily oxidized to iodine with iodosobenzene diacetate. Treatment of the 1,4-dimethoxynaphthalene with this reagent combination gave none of the desired iodide.

10. Evans, P. A.; Brandt, T. A. Unpublished Results.

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