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USING NBS AS A MILD BROMINATION REAGENT FOR POLYALKOXYAROMATIC SYSTEMS

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Abstract:—N-Bromosuccinimide in Methylene Chloride is A Mild Mono- or Di-bromination Reagent for Polyalkoxyaromatic Compounds Including Those Which are too Labile to be Brominated with Molecular Bromine.

Although N-bromosuccinimide(NBS) has long been used as a bromination agent, its usual application has been to allylic or benzylic bromination using radical initiators. Attempts to obtain regiocontrol under other conditions has presented some significant problems, as noted in one very recent publication in which a bromination system using NBS/HBF_4 for phenols and anisoles was developed[1] which was much more regioselective than previous techniques. The compounds which we desired to brominate were polymethoxy compounds of the sort which proved to be subject to demethylation and/or oxidation under relatively mild conditions as noted specifically below. Because of the electron-rich nature of the substrates, NBS in methylene chloride at low temperature and for extended periods was chosen, although simple anisoles react only very slowly with NBS in carbon tetrachloride, even at reflux[2].

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Simple substrates for bromination **1-3** are given in addition to the difficult cases **4-6** for comparison. Aside from 1, which was commercially available, literature preparations or readily applicable methods were available for **2**[3], **3**[4], **4**[5], **5**[6, 7], and **6**[8].

Results and Discussion

The results of our bromination studies are summarized in Table 1. Particular attention should be paid to the anthracene derivatives **5** and **6**, which with molecular bromine give demethylated and oxidized products. By the use of NBS in methylene chloride at ambient temperature, 1,4-dimethoxyanthracene **6** gives 85% of monobromo derivative **6a**, whereas with molecular bromine only 1,4-anthraquinone is isolated. Likewise, even with the more labile 1,2,3,4-tetrahydro-5,8,9,10-tetramethoxyanthracene **5**, which gives the tetrahydroanthracenedione with molecular bromine, by lowering the reaction temperature to 0^0C-10^0C we could obtain 75.6% of monobromo derivative **5a**. Even higher yields were possible with benzene and tetrahydronaphthalene derivatives **1** and **2** (92.7% and 95.0% respectively); however, we have not sought to truly optimize the reactions as yet. The method may be adapted to produce dibromo derivatives, thought the yields are all the 45-63% range, the best yield being obtained with 1,4-dimethoxy-naphthalene. The lowered yields may be attributed at least in part to greater steric requirement, once the first bromine has been introduced.

Experimental

NBS from Aldrich was used directly. ^{1}H NMR and ^{13}C NMR were recorded in

Table 1. Bromination of polyalkoxyaromatic compounds with NBS in methylene chloride

Polyalkoxyaromatic compounds		Time h	Products		Yield %
p-Dimethoxybenzene	**1**	20	2-Bromo-1,4-dimethoxybenzene	**1a**	93
		24	2,5-Dibromo-1,4-dimethoxybenzene	**1b**	50
5,6,7,8-Tetrahydro-1,4-dimethoxynaphthalene	**2**	20	2-Bromo-5,6,7,8-tetrahydro-1,4-dimethoxy-naphthalene	**2a**	95
		24	2,3-Dibromo-5,6,7,8-tetrahydro-1,4-dimethoxynaphthalene	**2b**	50
1,4-Dimethoxynaphthalene	**3**	5	2-Bromo-1,4-dimethoxynaphthalene	**3a**	88
		24	2,3-Dibromo-1,4-dimethoxynaphthalene	**3b**	63
1,4,5,8-Tetramethoxy-naphthalene	**4**	3	2-Bromo-1,4,5,8-tetramethoxy-naphthalene	**4a**	60
		24	2,6-Dibromo-1,4,5,8-tetramethoxy-naphthalene	**4b**	50
1,2,3,4-Tetrahydro-5,8,9,10-tetramethoxyanthracene	**5**	2*	6-Bromo-1,2,3,4-tetrahydro-5,8,9,10-tetramethoxyanthracene	**5a**	76
		2	6,7-Dibromo-1,2,3,4-tetrahydro-5,8,9,10-tetramethoxyanthracene	**5b**	49
1,4-Dimethoxyanthracene	**6**	3	2-Bromo-1,4-dimethoxyanthracene	**6a**	85
		4	2,3-Dibromo-1,4-dimethoxyanthracene	**6b**	45

*Reaction temperature is 0^0C-10^0C. Other reactions were carried out at room temperature.

$CDCl_3$ on a General Electric QE-300 at 300MHz and 75.48 MHz respectively with tetramethylsilane(TMS) as internal standard. Melting and boiling points were determined on a Thomas-Hoover melting point apparatus in open capillary tubes and were uncorrected.

2-Bromo-1,4-dimethoxynaphthalene 3a; General procedure:

In a typical reaction, 0.89g(5mmol) of NBS was added to a flask containing 0.94g(5mmol) of **3** in 30ml of methylene chloride, the mixture was stirred in room

temperature for 5 hours then washed with sodium sulfite and dried over anhydrous sodium sulfate. The dried solution was evaporated and the crude product was crystallized from aqueous ethanol, 1.18g (88.4%) of **3a** was obtained.

m.p. 56-57°C (lit.[9] 54-55°C)

^{1}H NMR δ 3.95(s, 3H), 3.97(s, 3H), 6.89(s, 1H), 7.47-7.59(m, 2H), 8.05-8.08(m, 2H), 8.19-8.22(m, 2H).

^{13}C NMR δ 55.9, 61.4, 107.9, 112.0, 121.8, 121.9, 122.6, 122.7, 125.8, 127.4, 129.0, 146.8, 152.3.

2,3-Dibromo-1,4-dimethoxynaphthalene 3b; General procedure:

In a typical reaction, 1.96g(11mmol) of NBS was added to a flask containing 0.94g(5mmol) of **3** in 30ml of methylene chloride, the mixture was stirred in room temperature for 24 hours then washed with sodium sulfite and dried over anhydrous sodium sulfate. The dried solution was evaporated and the crude product was crystallized in diethyl ether, 1.09g (62.9%) of **3b** was obtained.

m.p. 119-120°C (lit.[10] 119-121°C)

^{1}H NMR δ 4.04(s, 6H), 7.62-7.65(m, 2H), 8.14-8.17(m, 2H).

^{13}C NMR δ 61.5, 116.2, 122.7, 122.8, 127.4, 127.5, 128.2, 151.1.

2-Bromo-1,4-dimethoxybenzene[11] **1a**

b.p. 237°C

^{1}H NMR δ 3.76 (s, 3H), 3.84(s, 3H), 6.82-6.86(m, 2H), 7.12(d, J=2 Hz, 1H).

^{13}C NMR δ 55.8, 56.7, 112.8, 113.5, 118.9, 119.0, 150.2, 154.0.

2,5-Dibromo-1,4-dimethoxybenzene 1b

m.p. 135-137°C (lit.[12] 142°C)

^{1}H NMR δ 3.90(s, 6H), 7.15(s, 2H).

^{13}C NMR δ 57.0, 110.4, 117.0, 117.0, 150.4.

2-Bromo-5,6,7,8-tetrahydro-1,4-dimethoxynaphthalene [13] 2a

b.p. > 300°C

^{1}H NMR δ 1.77-1.81(m, 4H), 2.62(m, 2H), 2.81(m, 2H), 3.81(s, 3H), 3.83(s, 3H), 6.87(s, 1H).

^{13}C NMR δ 22.1, 22.3, 23.3, 24.4, 55.6, 60.1, 111.1, 113.0, 126.8, 133.3, 148.5, 154.0.

2,3-Dibromo-5,6,7,8-tetrahydro-1,4-dimethoxynaphthalene 2b

m.p. 112-113°C

^{1}H NMR δ 1.80-1.82(m, 4H), 2.77-2.83(m, 4H), 3.82(s, 6H).

^{13}C NMR δ 22:1, 24.2, 59.9, 117.4, 132.6, 152.4.

Elemental Analysis: Cal. C 41.18, H 4.03, Br 45.65. Found C 41.50, H 4.18, Br 43.17.

2-Bromo-1,4,5,8-tetramethoxynaphthalene 4a

m.p. 100-101°C (lit.[14] 104-105°C)

^{1}H NMR δ 3.87(s, 3H), 3.94(s, 3H), 3.98(s, 6H), 6.88-6.96(m, 2H), 7.05(s, 1H).

^{13}C NMR δ 57.1, 57.5, 57.6, 61.7, 108.6, 109.3, 111.3, 111.4, 115.3, 119.9, 123.5, 146.7, 149.8, 151.6, 153.5.

2,6-Dibromo-1,4,5,8-tetramethoxynaphthalene 4b

m.p. 212-214°C (lit. [14] 215-216°C)

^{1}H NMR δ 3.82(s, 6H), 3.97(s, 6H), 7.06(s, 2H).

^{13}C NMR 56.9, 61.8, 112.2, 115.3, 122.6, 147.0, 151.9.

6-Bromo-1,2,3,4-tetrahydro-5,8,9,10-tetramethoxyanthracene 5a

m.p. 132-133°C

^{1}H NMR δ 1.78-1.83(m, 2H), 2.90-2.95(m, 2H), 3.73(s, 3H), 3.75(s, 3H), 3.81(s, 3H), 3.95(s, 3H), 6.88(s, 1H).

^{13}C NMR δ 22.5, 23.7, 23.8, 56.6, 61.2, 61.4, 61.8, 109.2, 113.8, 120.1, 123.2, 130.4, 131.5, 145.6, 148.2, 150.1, 152.5.

Elemental Analysis: Cal. C 56.71, H 5.55, Br 20.96. Found C 56.59, H 5.66, Br 20.96.

6,7- Dibromo-1,2,3,4-tetrahydro-5,8,9,10-tetramethoxy-anthracene 5b

m.p. 143-145°C

^{1}H NMR δ 1.83(m, 4H), 2.94,(m, 4H), 3.75(s, 6H), 3.84(s, 6H).

^{13}C NMR δ 22.4, 23.9, 61.5, 61.8, 117.7, 122.3, 131.7, 148.6, 149.8.

Elemental Analysis: Cal. C 46.98, H 4.38, Br 34.73. Found C 46.91, H 4.43, Br 35.84.

2-Bromo-1,4-dimethoxyanthracene 6a

m.p. 79-80°C

^{1}H NMR δ 4.10(s, 3H), 4.11(s, 3H), 6.82(s, 1H), 7.52-7.60(m, 2H), 8.06-8.11(m, 2H), 8.65(s, 1H), 8.83(s, 1H).

^{13}C NMR δ 55.9, 61.4, 105.7, 110.8, 120.5, 120.6, 122.1, 122.2, 124.8, 125.8, 126.4, 127.1, 128.3, 128.4, 128.7, 128.8, 131.3, 132.3, 146.7, 152.3.

Elemental Analysis: Cal. C 60.59, H 4.13, Br 25.19. Found C 60.59, H 4.13, Br 25.9.

2,3-Dibromo-1,4-dimethoxyanthracene 6b

m.p. 164-66°C

^{1}H NMR δ 4.10(s, 3H), 7.55-7.58(dd J=7, 3Hz, 2H), 8.06-8.10(dd J=7, 3Hz, 2H), 8.69(s, 2H).

^{13}C NMR δ 61.4, 114.6, 121.9, 122.0, 126.3, 126.7, 128.5, 128.6, 132.2, 151.2.

Elemental Analysis: Cal. C 48.52, H 3.05, Br 40.35. Found C 48.11, H 3.12, Br 44.76.

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6. Compound **5** was prepared by reductive methylation of 1,2,3,4-tetrahydro-5,8-dihydroxy-9,10-anthracenedione. See ref. 4 and 7. m.p. 124-125^{0}C, ^{1}H NMR δ1.80(m, 4H), 2.94(m, 4H), 3.74(s, 6H), 6.78(s, 2H). ^{13}C NMR δ 22.64, 23.74, 56.91, 61.13, 105.69, 120.88, 130.08, 149.51, 150.10.

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A derivative of **2a** with an additional double bond (6-bromo-1,2-dihydro-5,8-dimethoxynaphthalene) was transformed into an anthracycline precursor by didehydrobenzene(benzyne) chemistry, see Khanapure, S. and Biehl, E.R. *Synthesis*, **1991**, 33.

We have prepared benzyne intermediates from a number of 1,2-dibromides including **2b** and **3b** by using lithium amalgam(J.L. Bloomer and Michael F.

Parker, unpublished), but until the appearance of Biehl's LDA method we had limited success in preparing benzynes from the monobromo series. A combination of selective monobromination and benzyne formation via LDA now appears to hold much promise for the construction of linear polycyclic arrays via intermediates **1a-6a**.

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The reported procedure yielded monobromide (44%), dibromide(17%) and unreacted starting material(3%), which have to be separated chromatographically. Our procedure gave monobromide in an improved yield(60%). We prepared **4** from naphthazarin using the "reductive methylation" procedure of Kraus(see reference 4).

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