N-Bromosuccinimide in Acetonitrile: A Mild and Regiospecific Nuclear Brominating Reagent for Methoxybenzenes and Naphthalenes

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During the past few years, we have investigated the use of homochiral sulfinylbenzoquinones[1] and naphthoquinones[2] in asymmetric Diels–Alder reactions. Most of these dienophiles were prepared by sulfinylation of bromo derivatives of 1,4-dimethoxybenzenes or -naphthalenes and further oxidation of the dimethoxy-substituted ring.[3] In connection with this project, we needed a mild method for the regioselective monobromination of the starting phenolic ethers. From the known brominating reagents for aromatic rings,[4] we selected *N*-bromosuccinimide, an available and popular reagent employed mostly in free radical allylic and benzylic brominations[5] but also for the electrophilic substitution of aromatic rings.[6,7] Several acid-catalyzed NBS ring brominations have been reported[7a] and continue to be of interest,[7b–d] mainly in connection with the bromination of polyalkylbenzenes. Seeking milder conditions, we focused on the use of NBS in CCl_4[5,6a,b,8] which has been employed on both aromatic ethers and polynuclear aromatic hydrocarbons. Despite the apparent utility of this reagent, it has not been widely used for nuclear brominations, which may be due to the variable results reported in terms of both products and yields. In this paper, we describe the high regioselectivity achieved in the ring bromination of several methoxy derivatives of benzene (**1a–e**) and naphthalene (**1f–j**) with NBS in CCl_4 and the substantial increase in reactivity observed using acetonitrile as solvent. We also report on the exclusive aromatic ring bromination of several methyl anisoles (**3a–e**) with NBS in CH_3CN, which strongly contrasts with the predominant benzylic bromination[9] observed for the same substrates in CCl_4. An important purpose of this paper is to refocus attention on the excellent ability of NBS to ring brominate activated aromatic compounds.

Methoxy aromatic derivatives **1** used in this study were either commercially available or already described in the literature (see the Experimental Section). Compounds **1a–j** were submitted to reaction with NBS in both CCl_4 and CH_3CN at different temperatures. The results are collected in Table 1. The products obtained under all conditions resulted exclusively from ring bromination. When benzylic positions (susceptible to radical halogenation) were present (compounds **1b–e**, entries 2–6), no benzyl bromides were detected in the crude reaction mixtures. In CCl_4, yields were excellent in all cases in which a reaction took place. The reaction exhibited complete regioselectivity with the presumably more electron rich aromatic ring positions[10] being the only ones affected by bromination.

Reactions of electron rich trimethoxybenzenes **1a–c** (entries 1–3) as well as 2-methyl-1,4-dimethoxybenzene (**1d**) (entry 4) took place at room temperature, with the exception of isopropyl derivative **1c** (entry 3) which required 30 min at reflux temperature.[11] The sole product was the 5-bromo derivative in all cases, which is evidence for a highly regioselective process fully controlled by both steric and electronic factors. Thus, the methyl group of **1d** or the more activating 2-methoxy group of **1a–1c** directed the bromination to the *para* position. Isopropyl derivative **1e** (entries 5 and 6) did not react even under refluxing conditions.[11] Methoxynaphthalenes **1f–j** also reacted with NBS–CCl_4, but most of them required refluxing (entries 7–13). Similar reactivity was exhibited by 1- and 2-methoxynaphthalenes (**1f** and **1g**) which yielded 4- and 1-bromo derivatives **2f** and **2g**, respectively (entries 7 and 8). 1,5-Dimethoxynaphthalene (**1h**) could be transformed into the mono- or dibrominated compound in a controlled manner. With 1.1 equiv of NBS, 4-bromo derivative **2h** was exclusively formed (entry 9), whereas 4,8-dibromo-1,5-dimethoxynaphthalene (**2h′**) was isolated in 88% yield upon reaction with 2.2 equiv (entry 10). Both mono- and dibromination reactions were highly regioselective. Compound **2h′** had been previously prepared[12] by reaction of **1h** with 2 equiv of Br_2 in refluxing CCl_4 in 58% yield. In our hands, this method yielded a mixture of regioisomers where **2h′** was the minor component which suggests that the low yield reported could be due to the lack of regioselectivity. This result is in contrast with the exclusive formation of **2h′** in high yield observed for the reaction with NBS.

The higher activation of 1,4,5-trimethoxynaphthalene (**1i**) allowed for the formation of bromo derivative **2i** at room temperature (entry 11). Finally, the treatment of 1,4,5,8-tetramethoxynaphthalene (**1j**) with 1 or 2 equiv of NBS yielded 2-bromo and 2,6-dibromo derivatives **2j** and **2j′**, respectively (entries 12 and 13), in a highly regioselective fashion. The apparently lower reactivity of **1j** (reflux was required) may be a consequence of its low solubility in CCl_4.

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(10) As indicated in ref 8, the bromination at the *para* position of the activating group is prefered with respect to the *ortho* position.

(11) The large size of the *i*-Pr group determines a decrease of the reactivity because it makes difficult the coplanarity of the flanking methoxy group with the subsequent decrease of its activating effect.

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Table 1. Bromination of Activated Aromatic Derivatives with 1.1 Equiv of NBS in CCl_4 and CH_3CN[a]

$$(MeO)_nAr \xrightarrow[CCl_4 \text{ or } CH_3CN]{NBS} (MeO)_nArBr$$
1 **2**

		CCl_4			CH_3CN			
entry	substrate	time (h)	T (°C)	yield (%)	time (h)	T (°C)	yield (%)	Br position
1	1,2,4-trimethoxybenzene (**1a**)	4	20	92				5-bromo (**2a**)
2	3-methyl-1,2,4-trimethoxybenzene (**1b**)	4	20	95				5-bromo (**2b**)
3	3-isopropyl-1,2,4-trimethoxybenzene (**1c**)	0.5	reflux	90	0.5	20	90	5-bromo (**2c**)
4	2-methyl-1,4-dimethoxybenzene (**1d**)	4	20	90				5-bromo- (**2d**)[b]
5	2-isopropyl-1,4-dimethoxybenzene (**1e**)	72	20	–	1	20	90	5-bromo- (**2e**)[b]
6	2-isopropyl-1,4-dimethoxybenzene (**1e**)	4	reflux	–				
7	1-methoxynaphthalene (**1f**)	24	reflux	92	2	20	94	4-bromo (**2f**)
8	2-methoxynaphthalene (**1g**)	24	reflux	90	3	20	92	1-bromo (**2g**)
9	1,5-dimethoxynaphthalene (**1h**)	12	reflux	85	2	20	89	4-bromo (**2h**)
10	1,5-dimethoxynaphthalene (**1h**)[c]	24	reflux	88	8	20	90	4,8-dibromo (**2h'**)
11	1,4,5-trimethoxynaphthalene (**1i**)	3	20	90				3-bromo- (**2i**)
12	1,4,5,8-tetramethoxynaphthalene (**1j**)	4	reflux	85	1	20	92	2-bromo (**2j**)
13	1,4,5,8-tetramethoxynaphthalene (**1j**)[c]	4	reflux	90	3	20	90	2,6-dibromo (**2j'**)

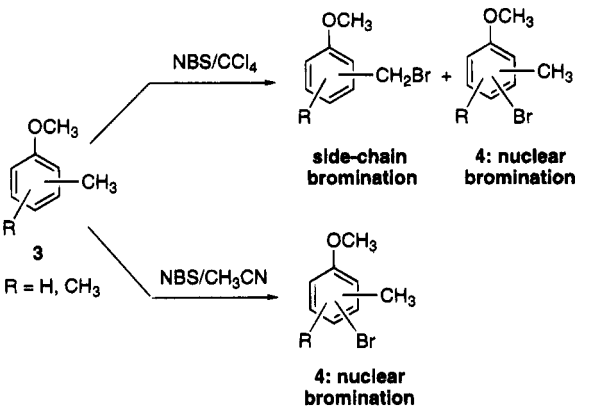
[a] Bold numbers given in parentheses are compound numbers. [b] This is not the correct IUPAC nomenclature for this compound (see the Experimental Section). [c] 2.2 equiv of NBS.

In accordance with previous work on the use of NBS for bromination of activated aromatic rings,[6,7] an electrophilic substitution mechanism must operate in these processes. The use of polar solvents such as propylene carbonate has been known to enhance the reactivity of NBS,[6c] making possible the ring bromination of polyalkylbenzenes. Nevertheless, competitive bromination of the solvent substantially decreased the yields of the ring bromination products. The NBS/DMF system[6e] was proven effective as a ring bromination reagent, but despite the simplicity of the operational procedure claimed by the authors, the elimination of DMF, a water miscible solvent with a high boiling point, presented difficulty.[13] Surprisingly, other polar media which could favor an ionic mechanism and would improve the reactivity of NBS as an electrophile have not been examined. We decided to investigate the influence of CH_3CN as a polar solvent with a low boiling point on the efficiency of NBS bromination in order to (i) achieve the reaction of **1e** that was not possible with NBS–CCl_4, (ii) effect the reaction under milder conditions in the cases where reflux was necessary, and (iii) increase the solubility of some less soluble substrates. All of these factors would improve the scope of NBS as a brominating agent.

The results obtained with the NBS/CH_3CN system are also collected in Table 1. In terms of reaction times, ring bromination with NBS was faster in CH_3CN than in CCl_4. For example, **1e** (unchanged in CCl_4, entry 5) reacted completely in 1 h at room temperature. All of the substrates that required reflux in CCl_4 were brominated at room temperature in CH_3CN in excellent yield (entries 3, 7–10, 12, and 13). In addition, the higher solubility of **1j** in CH_3CN allowed for a decrease in both the reaction time and temperature needed to achieve the ring bromination.

Two papers raising the question of nuclear versus side chain–bromination of methyl-substituted anisoles by NBS in CCl_4 recently appeared.[9,14] These papers focused on conditions to improve the side chain bromination of methyl anisoles (usually the main process with NBS–CCl_4) but did not address ring bromination. This competition could be the main reason of the sparse use of NBS in electrophilic brominations. Since we had observed a large increase in the ring bromination rate using CH_3CN as solvent (see Table 1), we decided to study the behavior of methylanisoles in order to determine whether the NBS/CH_3CN system could achieve ring bromination without competition from benzylic bromination. The results are presented in Scheme 1 and Table 2 (method B). For comparison, we also include results previously reported[9] for the same reactions using NBS–CCl_4 (method A).

Scheme 1



Several aspects of these results are noteworthy. Very different reactivity for NBS was observed with the two solvents. All anisoles showed almost exclusive preference for side chain bromination with NBS–CCl_4 in the presence of a light source (entries 1, 3, 5, 7, 9, and 11). Using CH_3CN as solvent in daylight, ring bromination products were the only ones detected (entries 2, 4, 6, 8, 10, and 12). Reactions were faster for substrates bearing no substituent *para* to the OMe group of the anisole (compare reaction times in entries 2 and 4 with that in entry 6). Even *ortho* bromination was favored over side chain bromination in the reaction of 4-methylanisole (**3c**) (entry 6). 2,6-Dimethylanisole (**3d**) gave only the 4-bromo derivative (entry 8), despite the presumed steric resonance inhibition exhibited by this substrate.[9] When 2,3-dimethylanisole (**3e**) was allowed to react with NBS–CCl_4, a mixture of the ring and side chain bromination products (entry 9) was formed, the major product being the result of benzylic bromination.[9] The NBS/CH_3CN

(13) We have detected this problem in our trial of the bromination of compound **1i**.

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Table 2. Distribution of Products of Ring and Side Chain Bromination of Substituted Anisoles[a]

entry	substrate	method[b]	ring bromination 2-Br	ring bromination 4-Br	side chain bromination	time (h)	yield (%)
1	2-methylanisole (**3a**)	A[c]			100		
2	2-methylanisole (**3a**)	B		100 (**4a**)		0.5	95
3	3-methylanisole (**3b**)	A[c]		8[d]	92		
4	3-methylanisole (**3b**)	B		100 (**4b**)		0.5	97
5	4-methylanisole (**3c**)	A[c]			100		
6	4-methylanisole (**3c**)	B	100 (**4c**)			3	95
7	2,6-dimethylanisole (**3d**)	A[c]			100		
8	2,6-dimethylanisole (**3d**)	B		100 (**4d**)		4	93
9	2,3-dimethylanisole (**3e**)	A[c]		3	97		
10	2,3-dimethylanisole (**3e**)	B		100 (**4e**)		0.5	94
11	4-bromo-2,3-dimethylanisole (**4e**)	A[c]			100		
12	4-bromo-2,3-dimethylanisole (**4e**)	B	100[e] (**4f**)			16	96

[a] Relative percentages of bromination products; bold numbers given in parentheses are compound numbers. [b] A: NBS–CCl_4 (reflux by light source) B: NBS (1.1 equiv)–CH_3CN (room temperature). [c] Data taken from ref 9. [d] When the reaction was conducted under reflux by heating with an oil bath, the ring bromination product increased to 25% (see ref 9). [e] 6-Bromo derivative.

system was extremely useful in this case, giving rise exclusively to 4-bromo-2,3-dimethylanisole (**4e**) at room temperature in 30 min and 94% yield (entry 10). Compound **4e** could be further brominated on the aromatic ring with NBS–CH_3CN to afford 4,6-dibromo-2,3-dimethylanisole (**4f**) (entry 12). This dibromination product was not detected when the reaction was carried out in CCl_4[9,14] (entry 11).

In conclusion, the regiospecific nuclear bromination of aromatic methoxy derivatives, including methylanisoles, can be efficiently achieved with NBS using CH_3CN as solvent. The absence of side chain bromination products in reactions conducted in CH_3CN suggests a substantial increase in the rate of the ionic process. This result broadens the range of application of NBS and provides a mild and controlled entry into polysubstituted aromatic bromoderivatives widely used in organic synthesis. We are currently extending this methodology to the use of *N*-halosuccinimides in the ring halogenation of activated aromatic compounds.

Experimental Section

IR spectra are given in cm^{-1}. ^1H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ at 200.1 and 50.3 MHz, respectively.

Materials. Anisoles **1a** and **3a–e** and methoxynaphthalenes **1f,g** were commercially available from Aldrich Chemical Co. Methoxybenzenes **1b**,[15] **1c**,[16] **1d**,[17] and **1e**[18] and methoxynaphthalenes **1h**,[19] **1i**,[20] and **1j**[12] were prepared by literature procedures.

General Procedure for the Nuclear Bromination of Aromatic Compounds with NBS. (1) In CCl_4. To a stirred solution of the aromatic compound (1 mmol) in 5 mL of CCl_4 was added NBS (see Table 1 for reaction conditions). After the reaction was complete, succinimide was filtered and washed with CCl_4 and the solvent evaporated under reduced pressure to obtain the pure brominated compound by ^1H-NMR.

(2) In CH_3CN. To a solution of the aromatic compound (1 mmol) in 5 mL of CH_3CN was added NBS (see Table 1 and Method B in Table 2 for reaction conditions). After the reaction was complete, the solvent was evaporated under reduced pressure and CCl_4 was added. The solid was filtered and washed with CCl_4 and the solvent eliminated to obtain the pure brominated compound by ^1H-NMR.

5-Bromo-1,2,4-trimethoxybenzene (2a):[21] ^1H-NMR δ 3.83, 3.86, 3.88 (9H, 3s), 6.58 (1H, s), 7.03 (1H, s).

5-Bromo-3-methyl-1,2,4-trimethoxybenzene (2b): IR ($CHCl_3$) 1000, 1090, 1210–1230, 1310, 1400, 1420, 1475, 2940; ^1H-NMR δ 2.24 (3H, s), 3.74, 3.77, 3.81 (9H, 3s), 6.91 (1H, s); ^{13}C-NMR δ 9.9, 55.9, 60.1, 60.2, 110.5, 113.3, 126.9, 147.0, 149.2, 149.6. Anal. Calcd for $C_{10}H_{13}BrO_3$: C, 46.00; H, 5.02; Br, 30.60. Found: C, 46.21; H, 5.04; Br, 30.21.

5-Bromo-3-isopropyl-1,2,4-trimethoxybenene (2c):[16] ^1H-NMR δ 1.33 (6H, d, J = 7.1 Hz), 3.46 (1H, sept, J = 7.1 Hz), 3.76, 3.81, 3.83 (9H, 3s), 6.94 (1H, s).

2-Bromo-5-methyl-1,4-dimethoxybenzene (2d):[22] ^1H-NMR δ 2.19 (3H, s), 3.79, 3.85 (6H, 2s), 6.76 (1H, s), 7.00 (1H, s).

2-Bromo-5-isopropyl-1,4-dimethoxybenzene (2e): IR ($CHCl_3$) 860, 1030, 1080, 1440, 1460, 1485, 2940; ^1H-NMR δ 1.20 (6H, d, J = 6.9 Hz), 3.27 (1H, sept, J = 6.9 Hz), 3.79, 3.87 (6H, 2s), 6.82 (1H, s), 7.03 (1H, s); ^{13}C-NMR δ 22.5, 26.9, 56.1, 56.9, 108.0, 110.9, 19.7, 137.3, 90.0, 91.2. Anal. Calcd for $C_{11}H_9BrO_2$: C, 50.98; H, 5.83; Br, 30.83. Found: C, 50.69; H, 6.10; Br, 30.62.

4-Bromo-1-methoxynapthalene (2f):[23] ^1H-NMR δ 3.94 (3H, s), 6.61 (1H, d, J = 8.3 Hz), 7.60 (2H, m), 7.68 (1H, d, J = 8.3 Hz), 8.30 (2H, m).

1-Bromo-2-methoxynaphthalene (2g):[24] ^1H-NMR δ 3.93 (3H, s), 7.9 (1H, d, J = 8.6 Hz), 7.32 (1H, ddd, J = 1.2, 6.9, and 8.1 Hz), 7.50 (1H, ddd, J = 1.2, 6.8, and 8.2 Hz), 7.71 (1H, d, J = 8.6 Hz), 7.70 (1H, m), 8.18 (1H, dd, J = 1.2 and 8.6 Hz).

4-Bromo-1,5-dimethoxynaphthalene (2h):[25] ^1H-NMR δ 3.87 and 3.89 (6H, 2s), 6.52 (1H, d, J = 7.1 Hz), 6.89 (1H, dd, J = 1.4 and 7.6 Hz), 7.34 (1H, t, J = 7.6 Hz), 7.60 (1H, d, J = 7.1 Hz), 7.87 (1H, dd, J = 1.4 and 7.6 Hz).

4,8-Dibromo-1,5-dimethoxynaphthalene (2h'):[12] ^1H-NMR δ 3.93 (6H, s), 6.74 (2H, d, J = 8.3 Hz), 7.71 (2H, d, J = 8.3 Hz).

3-Bromo-1,4,5-trimethoxynaphthalene (2i):[26] ^1H-NMR δ 3.78 (3H, s), 3.98 (6H, s), 7.06 (1H, s), 7.08 (1H, dd, J = 1.4 and 7.6 Hz), 7.45 (1H, t, J = 7.6 Hz), 7.82 (1H, dd, J = 1.4 and 7.6 Hz).

2-Bromo-1,4,5,8-tetramethoxynaphthalene (2j):[27] ^1H-NMR δ 3.82 and 3.89 (6H, 2s), 3.93 (6H, 1s), 6.85 and 6.90 (2H, AB system), 7.00 (1H, s).

2,6-Dibromo-1,4,5,8-tetramethoxynaphthalene (2j'):[27] ^1H-NMR δ 3.80 and 3.94 (12H, 2s), 7.05 (2H, s).

4-Bromo-2-methylanisole (4a):[28] ^1H-NMR δ 2.18 (3H, s), 3.80 (3H, s), 6.68 (1H, d, J = 9.3 Hz), 7.23–7.28 (2H, m).

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4-Bromo-3-methylanisole (4b):[29] ^{1}H-NMR δ 2.36 (3H, s), 3.76 (3H, s), 6.61 (1H, dd, J = 3.0 and 8.7 Hz), 6.78 (1H, d, J = 3.0 Hz), 7.39 (1H, d, J = 8.7 Hz).

2-Bromo-4-methylanisole (4c):[30] ^{1}H-NMR δ 2.27 (3H, s), 3.86 (3H, s), 6.79 (1H, d, J = 8.2 Hz), 7.06 (1H, dd, J = 2.2 and 8.2 Hz), 7.36 (1H, d, J = 2.2 Hz).

4-Bromo-2,6-dimethylanisole (4d):[31] ^{1}H-NMR δ 2.25 (6H, s), 3.70 (3H, s), 7.13 (2H, s).

4-Bromo-2,3-dimethylanisole (4e):[14] ^{1}H-NMR δ 2.18 and 2.34 (6H, 2s), 3.77 (3H, s), 6.57 (1H, d, J = 9.0 Hz), 7.32 (1H, d, J = 9.0 Hz).

4,6-Dibromo-2,3-dimethylanisole (4f):[32] ^{1}H-NMR δ 2.27 (6H, s), 3.72 (3H, s), 7.52 (1H, s).

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