A Mild Selective Monobromination Reagent System for Alkoxybenzenes; *N*-Bromosuccinimide-Silica Gel

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Synopsis. The monobromination of alkoxybenzenes with *N*-bromosuccinimide catalyzed by silica gel in carbon tetrachloride occurred preferentially at the para-position. *m*-*t*-Butylmethoxybenzene yielded 4-bromo-3-*t*-butyl-1-methoxybenzene with a selectivity of 74% even in the presence of a bulky substituent at the meta-position.

A variety of methods for the selective nuclear bromination of activated aromatic compounds has been developed in view of the importance of the brominated compound in organic syntheses. The monobromination of 1,3-dimethoxybenzenes was conducted using a dioxane-bromine complex.[1] The reagent is somewhat troublesome to use due to its hygroscopic property and thermal instability at room temperature.

Silica-gel-catalyzed chlorination of aromatic compounds has attracted much interest owing to its simplicity and selectivity.[2-5] Various types of chlorinating agents may be used. These studies prompted us to examine the silica-gel-catalyzed nuclear bromination of activated aromatic compounds with *N*-bromosuccinimide (NBS). Recently, the bromination of indoles and benzimidazoles with NBS-silica gel has been reported.[6] Here, we would like to describe a facile method for the selective monobromination of reactive alkoxybenzenes and to briefly discuss the role of silica gel in the reaction.

Results and Discussion

The results of bromination are summarized in Table 1. The reaction of *m*-dimethoxybenzene with a slight excess of NBS in carbon tetrachloride containing silica gel at 30 °C for 2 h gave 1-bromo-2,4-dimethoxybenzene in quantitative yield. No trace of the dibromo compound was detected. In the absence of silica gel, no bromination was observed. The rate of the reaction was largely dependent upon the amount of silica gel and the stirring speed. This was due to the heterogeneity of the reaction. A variety of silica gels showed the catalytic activity of bromination; an acidic silica gel (Microbead 3A, chromatographic material, Fuji-Davison) is very effective.

A similar treatment of *o*-dimethoxybenzene and 1-methoxynaphthalene gave monobrominated products in excellent yields. Methoxybenzene and ethoxybenzene required a longer time. The bromination is highly para-selective. Methoxybenzene gave a para-isomer of >98.5% purity. In the cases of substrates with a para-substituent, such as *p*-dimethoxybenzene and 2-methoxynaphthalene, ortho bromination occurred in moderate yields.

The reaction of *m*-dimethoxybenzene with 2.2 equivalent of NBS for 45 h gave 1,5-dibromo-2,4-dimethoxybenzene in 80% yield. In other cases, dibromination is of no practical value, due to the slow reaction.

In order to obtain some insight into the mechanism of bromination, the reaction of a series of *m*-alkylmethoxybenzenes was carried out. Electrophilic bromination with NBS in polar solvents has been reported,[7,8] and it was considered that NBS was activated on the polar silica-gel surface. It was expected that the regioselectivity of the bromination by a bulky electrophile is affected by a substituent at the meta position. However, the bromination of *m*-methyl-, *m*-ethyl-, and *m*-isopropylmethoxybenzenes occurred exclusively at the para-position to the methoxyl group. It was particularly noteworthy that *m*-*t*-butylmethoxybenzene yielded 4- and 6-bromo-3-*t*-butyl-1-methoxybenzene in a ratio of 74:26. These

Table 1. Bromination of Alkoxybenzenes with *N*-Bromosuccinimide/Silica Gel in Carbon Tetrachloride[a]

Alkoxybenzene	Time / h	Product	Yield / %
m-Dimethoxybenzene	2	1-Bromo-2,4-dimethoxybenzene	99
o-Dimethoxybenzene	4	4-Bromo-1,2-dimethoxybenzene	98
p-Dimethoxybenzene	24	2-Bromo-1,4-dimethoxybenzene	58
1-Methoxynaphthalene	4	4-Bromo-1-methoxynaphthalene	99
2-Methoxynaphthalene	18	1-Bromo-2-methoxynaphthalene	66
Methoxybenzene	20	*p*-Bromomethoxybenzene	90
Ethoxybenzene	40	*p*-Bromoethoxybenzene	96
m-Methylmethoxybenzene	40	4-Bromo-3-methyl-1-methoxybenzene	87
m-Ethylmethoxybenzene	20	4-Bromo-3-ethyl-1-methoxybenzene	90
m-Isopropylmethoxybenzene	20	4-Bromo-3-isopropyl-1-methoxybenzene	78
m-*t*-Butylmethoxybenzene	20	4- and 6-Bromo-3-*t*-butyl-1-methoxybenzene	85[b]

a) Substrate (2 mmol), NBS (2.1 mmol), Silica gel (Microbead 3A, 1g), CCl_4 (20 ml), 30°C.
b) Product distribution (4-/6-=74/26).

results were entirely unexpected, since electrophilic aromatic substitution at the ortho-position to a *t*-butyl group is highly suppressed due to its bulkiness.[9] Indeed, the iron-catalyzed bromination of *m*-*t*-butylmethoxybenzene yielded only 6-bromo-3-*t*-butyl-1-methoxybenzene. These findings imply that the steric repulsion between a *m*-alkyl substituent and a brominating species is not a dominant factor for controlling the isomer distribution.

Thallium(III)-induced bromination of meta-alkylmethoxybenzenes has been reported to be para selective.[10] The formation of 4-bromo-3-*t*-butyl-1-methoxybenzene with ca. 40% selectivity was attributed to the electronic control. In the present system, NBS is slightly polarized on the silica-gel surface; it can, therefore, be presumed that the brominating species has a considerable soft character. The regioselectivity in the electrophilic aromatic substitution by soft electrophiles is determined by the frontier electron density,[11] the reaction is expected to occur preferentially at the para-position for the methoxybenzene.

The regioselectivity is affected by the nature of the silica gels. Neutral and basic silica gels gave somewhat better selectivity, though the conversion was lower than that catalyzed by Microbead 3A. The silica gel, conversion/% at 10 h, and the selectivity for the 4-bromo-3-*t*-butyl-1-methoxybenzene were follows: Microbead 3A, 97, 74; Microbead 4B (neutral, Fuji-Davison), 62, 79; Microbead 5D (basic, Fuji-Davison), 51, 86; Wakogel C-300 (Wako Chemicals), 38, 84; Kieselgel 60 (Merck), 51, 82.

The commercial availability of the reagent, simple reaction conditions, no evolution of hydrogen bromide and excellent yields of the monobrominated products make our method valuable from a preparative point of view.

Experimental

N-Bromosuccinimide was recrystallized from water and dried over phosphorus pentaoxide. Silica gels were used as received. The bromination was conducted in the dark. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL GX-270 spectrometer in $CDCl_3$ operating at 270 and 67.9 MHz with tetramethylsilane as an internal standard. IR spectra were obtained with a JASCO IRA-1 spectrophotometer. GC-MS measurements were carried out on a Hitachi M-52 mass spectrometer. The IR and mass spectral properties of the products were in accord with the assigned structure. Analytical gas chromatography was performed on a Yanagimoto G-180 with a flame ionization detector using 3 m×3 mm Silicone OV-17(2%)/Chromosorb W, Silicone DC-560 (10%)/Chromosorb W, and PEG 20M(25%)/Shimalite columns. The GLPC analyses of the isolated products indicated the purity of >98%.

Silica-Gel-Catalyzed Bromination of *m*-Dimethoxybenzene with NBS: A Typical Procedure: To a solution of *m*-dimethoxybenzene (276 mg, 2 mmol) in carbon tetrachloride (20 ml) were added *N*-bromosuccinimide (374 mg, 2.1 mmol) and Microbead 3A (1.00 g). The mixture was vigorously stirred at 30 °C for 2 h. The insoluble material was removed by filtration, washed with aqueous sodium thiosulfate, and dried over anhydrous sodium sulfate. Filtration, removal of the solvent, and Kugelrohr distillation (bath temperature 133 °C, 2.7 kPa) yielded 433 mg (99%) of 1-bromo-2,4-dimethoxybenzene. ^{1}H NMR ($CDCl_3$); δ=3.862 (MeO), 3.897 (MeO), 6.393 (H-5, dd, J_{35}, 2.4 Hz, J_{56}, 8.7 Hz), 6.482 (H-3, d), 7.398 (H-6, d).

4-Bromo-1,2-dimethoxybenzene (135 °C, 2.7 kPa). ^{1}H NMR ($CDCl_3$); δ=3.834 (MeO), 3.867 (MeO), 6.732 (H-6, d, J_{56}, 8.6 Hz), 6.976 (H-3, d, J_{35}, 2.3 Hz), 7.029 (H-5, dd).

2-Bromo-1,4-dimethoxybenzene (133 °C, 2.7 kPa). ^{1}H NMR ($CDCl_3$); δ=3.758 (MeO), 3.842 (MeO), 6.81 (H-5 and H-6, m), 7.116 (d, J_{45}, 2.6 Hz).

4-Bromo-1-methoxynaphthalene (105 °C, 25 Pa). ^{1}H NMR ($CDCl_3$); δ=3.920 (MeO), 6.617 (H-2, d, J_{23}, 8.0 Hz), 7.50 (H-7, m), 7.59 (H-6, m), 7.628 (H-3, d), 8.148 (H-5, d, J_{56}, 8.0 Hz), 8.250 (H-8, d, J_{78}, 8.0 Hz).

1-Bromo-2-methoxynaphthalene (110 °C, 30 Pa). ^{1}H NMR ($CDCl_3$); δ=4.008 (MeO), 7.250 (H-3, d, J_{34}, 9.0 Hz), 7.38 (H-6, m), 7.55 (H-7, m), 7.757 (H-5, d, J_{56}, 8.0 Hz), 7.788 (H-4, d), 8.216 (H-8, d, J_{78} 8.7 Hz).

***p*-Bromomethoxybenzene** (120 °C, 3.3 kPa). ^{1}H NMR ($CDCl_3$); δ=3.756 (MeO), 6.76 and 7.36 (AA'BB').

***p*-Bromoethoxybenzene** (123 °C, 3.0 kPa). ^{1}H NMR ($CDCl_3$); δ=1.399 (CH_3, t, *J* 6.9 Hz), 3.990 (CH_2, q) 6.75 and 7.34 (AA'BB').

4-Bromo-3-methyl-1-methoxybenzene (123 °C, 3.3 kPa). ^{1}H NMR ($CDCl_3$); δ=2.360 (CH_3), 3.765 (MeO), 6.607 (H-6, dd, J_{56}, 8.6 Hz, J_{26}, 3.0 Hz), 6.781 (H-2, d), 7.391 (H-5, d).

4-Bromo-3-ethyl-1-methoxybenzene (112 °C, 1.9 kPa). ^{1}H NMR ($CDCl_3$); δ=1.212 (CH_3, t, *J*, 7.5 Hz), 2.713 (CH_2, q), 3.781 (MeO), 6.615 (H-6, dd, J_{56}, 8.6 Hz, J_{26}, 3.0 Hz), 6.786 (H-2, d), 7.269 (H-5, d).

4-Bromo-3-isopropyl-1-methoxybenzene (116 °C, 2.1 kPa). ^{1}H NMR ($CDCl_3$); δ=1.228 (CH_3, d, *J*, 6.9 Hz), 3.310 (CH, sep), 3.788 (MeO), 6.606 (H-6, dd, J_{26} 2.9 Hz, J_{56} 8.7 Hz), 6.826 (H-2, d), 7.411 (H-5, d).

6-Bromo-3-*t*-butyl-1-methoxybenzene: To a mixture of *m*-*t*-butylmethoxybenzene (20 mmol) and a trace amount of iron powder was added a solution of bromine (20 mmol) in carbon tetrachloride (20 ml). The mixture was stirred for 2 h, and poured into water (50 ml). After the conventional work-up, 6-bromo-3-*t*-butyl-1-methoxybenzene was obtained by Kugelrohr distillation (125 °C, 2.0 kPa) in 85% yield. ^{1}H NMR ($CDCl_3$); δ=1.314 (*t*Bu), 3.900 (MeO), 6.857 (H-4, dd, J_{24}, 2.2 Hz, J_{45}, 8.3 Hz), 6.918 (H-2, d), 7.425 (H-5, d). ^{13}C NMR ($CDCl_3$); δ=31.1 (q), 34.7 (s), 55.9 (q), 108.3 (C-6, s), 109.5 (C-2, d), 118.8 (C-4, d), 132.4 (C-5, d), 152.0 (C-3, s), 155.2 (C-1. s).

Bromination of *m*-*t*-Butylmethoxybenzene with NBS-Silica Gel: Silica-gel-catalyzed bromination was carried out in a similar manner as described above for 20 h. ^{1}H and ^{13}C NMR analysis of the distillate indicated that it consisted of two components in a ratio of 74:26. The NMR spectral data of the minor component was identical with those of 6-bromo-3-*t*-butyl-1-methoxybenzene. On the basis of the ^{1}H and ^{13}C NMR data, the major component was assigned to 4-bromo-3-*t*-butyl-1-methoxybenzene: ^{1}H NMR ($CDCl_3$) δ= 1.492 (*t*Bu), 3.781 (MeO), 6.577 (H-6, dd, J_{26}, 3.2 Hz, J_{56}, 8.7 Hz), 6.997 (H-2, d), 7.465 (H-5, d). ^{13}C NMR ($CDCl_3$); δ=29.6 (q), 36.6 (s), 55.3 (q), 111.5 (C-6, d), 113.0 (C-4, s), 115.3 (C-2, d), 136.1 (C-5, d), 148.9 (C-3, s), 158.6 (C-1, s).

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