Halogenation Using *N*-Halogenocompounds. II. Acid Catalyzed Bromination of Aromatic Compounds with 1,3-Dibromo-5,5-dimethylhydantoin[1)]

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Ring bromination of aromatic compounds using 1,3-dibromo-5,5-dimethylhydantoin in dichloromethane is promoted by the addition of strong acids. Both organic and inorganic acids whose pK_a values are lower than −2 showed the promoting effect. This acid-catalyzed bromination is both practical and effective, even for aromatics having electron-withdrawing substituents.

The selective ring or side-chain bromination of aromatic compounds with *N*-bromo compounds, such as *N*-bromosuccinimide (NBS), 1,3-dibromo-5,5-dimethylhydantoin (DBMH), has been an attractive theme for organic chemists for a long time,[2)] and many suggestions concerning aromatic ring bromination have been offered. Schmid[3)] found that ring bromination with NBS is catalyzed by Lewis acids, such as the chlorides of aluminum, zinc, and iron. This method is unsuitable for aromatic compounds containing hetero atoms, which form complexes with the Lewis acid. The *N*-bromoacetanilide–carboxylic acids system[4)] and the NBS–DMF system[5)] were proposed for the ring bromination of reactive aromatic compounds. Recently, the bromination of anisole with NBS mediated by silica gel has been reported.[6,7)] Lambert et al. reported on the bromination of benzene and toluene using the NBS–H_2SO_4–H_2O system.[8)] This method has a defect in that the hydrocarbons must be used in large excess as the solvent as well as the substrates. We wish to report on a convenient ring bromination of aromatic compounds, including strongly deactivated ones, in the DBMH–acid system.

Results and Discussion

The results of bromination of toluene with the DBMH–CH_3SO_3H system in chlorinated methanes are summarized in Table 1. Dichloromethane and chloroform were found to be better as the solvents in this reaction than carbon tetrachloride, which has been most commonly used in brominations with NBS.[2)] This result seems to be caused by the limited solubility of DBMH in carbon tetrachloride. We used dichloromethane as the solvent in the bromination described hereafter due to its easy handling and higher dissolving power for DBMH.

Table 2 shows the results of bromination of toluene with DBMH or NBS at room temperature in the presence of various acids in the dark. The products were only monobromotoluenes (*ortho* and *para*); dibromotoluenes or benzyl bromide was not detected in all cases.

Table 1. Bromination of Toluene in Chlorinated Methanes with DBMH–CH_3SO_3H System in the Dark[a)]

		Bromotoluene[b)]	Recovery[b)]
Solvent	Temp	% (*o*/*p*)	%
CH_2Cl_2	R.T.	69.5(1.2)	30.5
CH_2Cl_2	Reflux	86.9(1.2)	13.1
$CHCl_3$	R.T.	84.3(1.1)	15.7
$CHCl_3$	Reflux	93.3(1.2)	6.7
CCl_4	R.T.	3.0(1.1)	97.1
CCl_4	Reflux	30.3(1.5)	69.7

a) Molar ratio of toluene/acid/DBMH is 1/0.5/0.5. Reaction time is 2 h. b) Determined by GC analysis.

All strong acids having pK_a values[9)] lower than ca. −2, promoted bromination with DBMH. They include both organic (e.g., CF_3SO_3H, $PhSO_3H$, and CH_3SO_3H) and inorganic acids (e.g., $HClO_4$ and H_2SO_4). Weak acids as well as a solid acid (Nafion®) were ineffective. DBMH has been clearly shown to be more active than NBS. An attempt to brominate toluene with bromine under similar acidic conditions failed, and the substrate was recovered quantitatively.

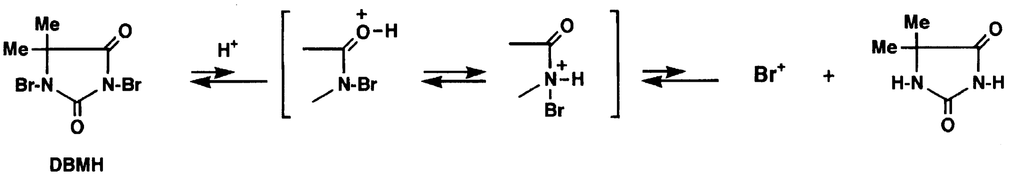
The mechanism of the ring bromination is presumed to be as follows: (1) The brominating reagents are protonated in the presence of a strong acid; (2) the protonated species generate the bromonium ion; and (3) the ion is attacked by aromatic rings (Scheme 1).

This DBMH (0.5 mol)–acid system was applied to the bromination of various aromatic compounds (1 mol). The results are given in Table 3. It is especially noteworthy that even deactivated substrates, such as nitrobenzene, trifluoromethylbenzene, methylbenzoate, and 4-nitrotoluene, were brominated at the *meta* position of the electron-withdrawing substituents in 76—96% yields when they were refluxed in DBMH (0.5 mol)–H_2SO_4 (1 mol)–CH_2Cl_2. Other methods to obtain these products require complicated procedures[10)] or carefully controlled conditions.[11)] Halobenzenes were

Table 2. Effect of Acid on Bromination of Toluene with DBMH and NBS in CH_2Cl_2[a)]

Acid[b)]	pK_a[c)]	DBMH[d)] Bromotoluenes[f)]	DBMH[d)] Recovery[f)]	NBS[e)] Bromotoluenes[f)]	NBS[e)] Recovery[f)]
		% (*o*/*p*)	%	% (*o*/*p*)	%
None		0	100	0	100
CF_3SO_3H	−5.1	94.0 (1.1)	6.0	32.8 (0.7)	67.2
$PhSO_3H$	−2.8	83.6 (1.3)	16.4	11.3 (1.5)	88.7
CH_3SO_3H	−1.9	69.5 (1.2)	30.5	11.4 (1.4)	88.6
CF_3COOH	−0.6	53.4 (0.6)	46.6	0	100
PhCOOH	4.2	0	100	0	100
CH_3COOH	4.76	0	100	0	100
$HClO_4$	−5.0	87.3 (1.5)	12.6	21.0 (2.1)	79.0
H_2SO_4	−2.8	64.0 (1.4)	35.9	3.1 (1.6)	96.9
H_3PO_4	2.1	4.5 (2.0)	95.5	0.4 (3.0)	99.6
Nafion H[g)]		0	100	0.3 (1.5)	99.7

a) Reaction was carried out at room temperature for 2 h in the dark. b) Molar ratio of an acid to toluene was 0.5. c) See Ref. 9. d) Molar ratio of DBMH to toluene was 0.5. e) Molar ratio of NBS to toluene was 1.0. f) Determined by GC analysis. g) Nafion H : Toluene=1 : 1 (w/w).



Scheme 1.

converted to the corresponding bromohalobenzenes in a reaction using DBMH–H_2SO_4 under refluxing conditions. The yield of bromobenzene increased from 69 to 84% upon changing H_2SO_4 to CF_3SO_3H in the reaction of benzene. Anisole, *o*-methoxytoluene, 2-methoxynaphthalene, and acenaphthene were brominated to *p*-bromoanisole, 3-bromo-6-methoxytoluene, 1-bromo-2-methoxynaphthalene, and 5-bromoacenaphthene, respectively, in 83—99% yields in the presence of a catalytic amount (0.1 mol) of CF_3SO_3H, CH_3SO_3H or H_2SO_4 at 30 °C. *o*-Bromoanisole was not detected in the reaction of anisole. Naphthalene, phenanthrene, and fluorene were converted to the corresponding monobromides in high yields by being treated with DBMH in the presence of CH_3SO_3H, H_2SO_4 or CF_3SO_3H. One molar amount of CF_3SO_3H or H_2SO_4 was needed to dibrominate the 2,7-positions of fluorene by the use of 1 molar amount of DBMH. The bromination of *m*-dinitrobenzene and *m*-bromonitrobenzene, which have two deactivating groups, were attempted. The former was unsuccessful, and in the latter the yield of 2,5-dibromonitrobenzene was no more than 39%. All of the reactions noted in Tables 1, 2, and 3 were carried out in the dark in order to avoid any side-chain bromination (allylic bromination).

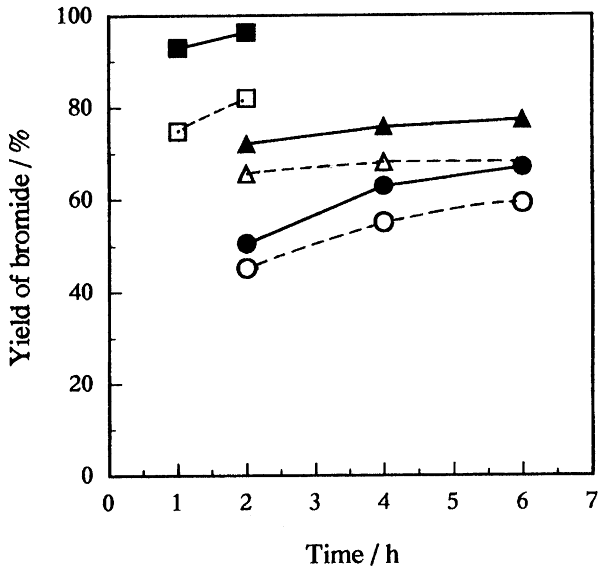


Fig. 1. Time dependence of product yield in the bromination of aromatic compounds with DBMH–Acid in the light or in the dark: *p*-nitrotoluene+100 mol% CF_3SO_3H (□ light, ■ dark), benzene+50 mol% CH_3SO_3H (△ light, ▲ dark), nitrobenzene+100 mol% CF_3SO_3H (○ light, ● dark).

Figure 1 shows examples of the time dependence of the product yield in the bromination of benzene, nitrobenzene, and *p*-nitrotoluene under irradiation with a tungsten lamp or in the dark in the presence of CF_3SO_3H or CH_3SO_3H. This figure shows that the yields of the brominated products were lower in the light than in the dark. A hindrance of ring bromina-

Table 3. Bromination of Aromatic Compounds with DBMH in the Presence of Acids in the Dark

		Molar ratio	React. condition			
Substrate	Acid	Substrate/Acid/DBMH	Temp	Time	Product/%[a]	
$C_6H_5NO_2$	CF_3SO_3H	1/1/0.5	30 °C	24 h	*m*-$O_2NC_6H_4Br$	87.1[78][b]
	H_2SO_4	1/1/0.5	Reflux	24 h	*m*-$O_2NC_6H_4Br$	75.2
$C_6H_5CF_3$	CF_3SO_3H	1/1/0.5	30 °C	15 h	*m*-$F_3CC_6H_4Br$	85.9
	H_2SO_4	1/1/0.5	Reflux	24 h	*m*-$F_3CC_6H_4Br$	81.3[72][b]
$C_6H_5CO_2Me$	CF_3SO_3H	1/1/0.5	30 °C	2 h	*m*-$MeOCOC_6H_4Br$	76.7
	H_2SO_4	1/1/0.5	Reflux	6 h	*m*-$MeOCOC_6H_4Br$	71.1
p-$MeC_6H_4NO_2$	CF_3SO_3H	1/1/0.5	30 °C	2 h	2-Me-5-$O_2NC_6H_3Br$	96.3[89][b]
	H_2SO_4	1/1/0.5	Reflux	6 h	2-Me-5-$O_2NC_6H_3Br$	84.1
C_6H_5F	H_2SO_4	1/0.5/0.5	Reflux	2 h	*o*- & *p*-FC_6H_4Br	85.0
C_6H_5Cl	H_2SO_4	1/0.5/0.5	Reflux	4 h	*o*- & *p*-ClC_6H_4Br	86.3
C_6H_5Br	H_2SO_4	1/0.5/0.5	Reflux	2 h	*o*- & *p*-$Br_2C_6H_4$	83.2
C_6H_6	CF_3SO_3H	1/0.5/0.5	Reflux	2 h	C_6H_5Br	83.6
	H_2SO_4	1/0.5/0.5	Reflux	2 h	C_6H_5Br	68.6
C_6H_5OMe	CF_3SO_3H	1/0.1/0.5	30 °C	5 min	*p*-$MeOC_6H_4Br$	97.4
	H_2SO_4	1/0.1/0.5	30 °C	15 min	*p*-$MeOC_6H_4Br$	97.2
o-MeC_6H_4OMe	CF_3SO_3H	1/0.1/0.5	30 °C	15 min	4-MeO-3-MeC_6H_3Br	99.5
	H_2SO_4	1/0.1/0.5	30 °C	15 min	4-MeO-3-MeC_6H_3Br	98.7
2-$MeOC_{10}H_7$	CH_3SO_3H	1/0.1/0.5	30 °C	30 min	1-Br-2-MeO-$C_{10}H_6$	98.8[87][b]
	H_2SO_4	1/0.1/0.5	30 °C	30 min	1-Br-2-MeO-$C_{10}H_6$	96.6
Acenaphthene	CH_3SO_3H	1/0.1/0.5	30 °C	15 min	5-Br-acenaphthene	87.1[82][b]
	H_2SO_4	1/0.1/0.5	30 °C	15 min	5-Br-acenaphthene	83.3
Naphthalene	CH_3SO_3H	1/1/0.5	30 °C	4 h	1-$BrC_{10}H_7$	83.2
	H_2SO_4	1/1/0.5	30 °C	2 h	1-$BrC_{10}H_7$	80.4
Phenanthrene	CF_3SO_3H	1/1/0.5	30 °C	2 h	9-Br-phenanthrene	90.3[80][b]
	H_2SO_4	1/1/0.5	30 °C	2 h	9-Br-phenanthrene	75.9
Fluorene	CF_3SO_3H	1/0.1/0.5	30 °C	1 h	2-Br-fluorene	79.7[62][b]
	H_2SO_4	1/0.1/0.5	30 °C	1 h	2-Br-fluorene	62.4
	CH_3SO_3H	1/0.5/0.5	30 °C	1 h	2-Br-fluorene	75.5
Fluorene	CF_3SO_3H	1/1/1	30 °C	3 h	2,7-Br_2-fluorene	95.0[73][b]
	H_2SO_4	1/1/1	30 °C	3 h	2,7-Br_2-fluorene	82.7

a) Determined by GC analysis. b) Isolated yield.

tion due to irradiation was also observed in some other cases. When toluene and DBMH–CF_3SO_3H (0.5 mol) in dichloromethane were irradiated with a lamp at room temperature, benzyl bromide and a mixture of *o*- and *p*-bromotoluene were obtained in 22 and 57% yields, respectively. The bromination of *p*-nitrotoluene with DBMH–CF_3SO_3H (1 mol) in the dark for 2 h afforded 96% of 2-bromo-4-nitrotoluene, while, a reaction in the light afforded 82% of the same product as well as a trace of 4-nitrobenzyl bromide. When the substrate was treated with DBMH–CF_3SO_3H (0.1 mol) for 4 h in light, the benzylic bromide was obtained in 55% yield, and 45% of the substrate was recovered.

The reaction mixture turned reddish brown within a few minutes when irradiated. This coloring suggests the formation of bromine. As described before, bromine cannot brominate even toluene. The yield of bromobenzene did not increase any further when a mixture of benzene, DBMH, and CF_3SO_3H (0.5 mol) was stirred for another 2 h in the dark after 2 h's irradiation. In contrast to this, the yield of bromobenzene gradually increased, even after 4 h's of stirring in the dark. These results support the assumption that ring bromination is retarded by a radical decomposition of the brominating agent (DBMH) caused by irradiation. The yield of *m*-bromonitrobenzene in the reaction of nitrobenzene in room light was about 15% lower than that in the dark. Room light did not influence the rapid bromination of an active substrate, such as alkoxybenzenes.

Based on Walling's report that the photobromination of dichloromethane by NBS gives bromodichloromethane,[12] it is assumed that the bromo-radical is formed by the decomposition of DBMH in light, and reacts with dichloromethane, which is the solvent. Moreover, the bromo-radical is inferred to react with a side-chain of an aralkyl compound as well as the solvent when such a substrate is present. Thus, the radical decomposition of DBMH lowers the yields of ring-brominated compounds. It is not yet clear whether the bromo-radical is formed from DBMH or from the protonated DBMH.

In conclusion, because of its mild reaction conditions, simple experimental operations, and generally excellent yields of ring brominated compounds, our method is practical for a wide variety of aromatic brominations, especially deactivated compounds.

Experimental

The melting and boiling points are uncorrected. The reagents and solvents were purchased and used without purification. A part of the DBMH was prepared by our method;[13] the remainder was purchased. Analyses of the products were performed on a HITACHI Gas Chromatograph (263-30) equipped with a 30 m×0.25 mm i.d. fused-silica capillary column (TC-1701). 1-Bromo-2-methoxynaphthalene, 5-bromoacenaphthene, 9-bromophenanthrene, 2-bromofluorene, 2,7-dibromofluorene, 1-bromo-3-(trifluoromethyl)benzene, *m*-bromonitrobenzene, 2-bromo-4-nitrotoluene were isolated and identified by their mp and NMR spectra. 1-Bromo-4-methoxy-3-methylbenzene was identified based on an the authentic sample prepared by the reported procedure.[14] Identification of the other products was carried out by using the purchased samples.

Analytical-Scale Bromination in the Dark. The bromination of toluene was typical. To a solution of toluene (270 mg, 3 mmol) and CH_3SO_3H (144 mg, 1.5 mmol) in CH_2Cl_2 (6 ml) was added DBMH (429 mg, 1.5 mmol) at once. The mixture was stirred for 2 h at room temperature in the dark. An aqueous saturated solution of sodium hydrogensulfite was added to the reaction mixture until the orange organic layer was decolorized. The mixture was neutralized by the addition of a 2 M aqueous sodium carbonate solution (1 M=1 mol dm^{-3}). The organic layer was separated, dried over anhydrous $MgSO_4$, and submitted to GC analysis.

Analytical-Scale Bromination in the Light. The bromination of *p*-nitrotoluene was typical. A mixture of *p*-nitrotoluene (411 mg, 3 mmol), CF_3SO_3H (450 mg, 3 mmol), and DBMH (429 mg, 1.5 mmol) in CH_2Cl_2 (6 ml) was directly irradiated for 2 h at room temperature with a 200-W tungsten lamp. The reaction mixture was worked up as described above and analyzed by GC.

Synthetic Scale Bromination in the Dark. The bromination of *p*-nitrotoluene was typical. A mixture of *p*-nitrotoluene (1.37 g, 10 mmol), CF_3SO_3H (1.80 g, 12 mmol), and DBMH (1.72 g, 6 mmol) in CH_2Cl_2 (20 ml) was stirred for 2 h at room temperature in the dark. The reaction mixture was worked up as described in the analytical-scale bromination. The organic solution obtained was concentrated. The residue was recrystallized from hexane to give 1.9 g (89% yield) of 2-bromo-4-nitrotoluene: colorless needles, mp 76.0—77.0 °C (lit,[15] mp 77.5 °C).

***m*-Bromonitrobenzene:** Yield, 78%: colorless needles (hexane); mp 53—54 °C (lit,[16] mp 56 °C).

1-Bromo-3-(trifluoromethyl)benzene: Yield, 72%: bp 151—153 °C (lit,[17] bp 151—152 °C).

1-Bromo-2-methoxynaphthalene: Yield, 87%: colorless plates (hexane); mp 85—86 °C (lit,[18] mp 85 °C).

5-Bromoacenaphthene: Yield, 82%: colorless needles (hexane); mp 50—52 °C (lit,[5] mp 54—55 °C).

9-Bromophenanthrene: Column chromatography (silica gel, hexane) gave 80% yield of 9-bromophenanthrene, colorless prisms (hexane): mp 62.0—63.0 °C (lit,[19] mp 63.8—64.8 °C).

2-Bromofluorene: Yield, 62%: colorless plates (hexane): mp 105—106 °C (lit,[20] mp 102—103 °C).

2,7-Dibromofluorene: Yield, 73%: colorless needles (hexane); mp 161—163 °C (lit,[20] mp 165—166 °C).

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