Halogenation Using Quaternary Ammonium Polyhalides. XIV.[1) Aromatic Bromination and Iodination of Arenes by Use of Benzyltrimethylammonium Polyhalides–Zinc Chloride System

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The reaction of arenes with benzyltrimethylammonium tribromide or benzyltrimethylammonium dichloroiodate in acetic acid in the presence of $ZnCl_2$ at room temperature or at 70 °C gave bromo- or iodo-substituted arenes in good yield, respectively.

The aromatic bromination of arenes (**1**) with molecular bromine has usually been brought about in the presence of a catalytic amount of iodine or iron filings.[2)] The reaction of **1** with NBS and aqueous sulfuric acid gives bromo-substituted arenes (**2**).[3)] Reactive **1** can be (mono)brominated by the use of NBS in DMF.[4)] Trifluoroacetyl hypobromite (CF_3COOBr),[5)] which is prepared by a reaction of bromine with silver trifluoroacetate, and copper(II) bromide[6)] have also been used as brominating agents for arenes.

A direct iodination of **1** using I_2 can be accomplished with the use of HNO_3[7)] or HIO_3/H_2SO_4[8)] to oxidize HI to I_2 and so displace the equilibrium. A mixture of I_2 and $HIO_4 \cdot 2H_2O$ is conveniently used for the direct iodination of polyalkylbenzenes.[9)] Iodoarene (**3**) have also been synthesized by a reaction of **1** with I_2 and an equimolecular mixture of $AlCl_3$ and $CuCl_2$.[10)] Activated **1** can be iodinated by the use of I_2 and $Cu(OAc)_2$ in acetic acid.[11)]

We have recently shown that quaternary ammonium polyhalides, such as benzyltrimethylammonium tribromide (BTMA Br_3)[12)] or benzyltrimethylammonium dichloroiodate (BTMA ICl_2),[13)] are useful brominating or iodinating agents for reactive aromatic compounds. In this paper, we wish to report on the bromination and iodination of **1** by the use of BTMA Br_3-$ZnCl_2$ and BTMA ICl_2-$ZnCl_2$, respectively.

Results and Discussion

The reaction of **1** with a calculated amount of BTMA Br_3 and $ZnCl_2$ or BTMA ICl_2 and $ZnCl_2$ in acetic acid (at room temperature or at 70 °C) gave **2** or **3** in good yields, respectively. The results are summarized in Table 1.

While such reactive aromatic compounds as phenols, aromatic amines, aromatic ethers, and acetanilides have been easily brominated by BTMA Br_3 in dichloromethane in the presence of methanol, the reaction of **1** (less reactive compounds) with BTMA Br_3 in dichloromethane-methanol did not proceed at all, even under reflux for many hours. However, **1** could be smoothly brominated by use of this reagent in acetic acid with the aid of the Lewis acid $ZnCl_2$. Thus, the combined effect of BTMA Br_3 and $ZnCl_2$ in acetic acid provides a new excellent bromination procedure for **1**.

BTMA ICl_2 is slightly soluble in acetic acid at room temperature. However, an addition of $ZnCl_2$ makes this reagent soluble in acetic acid, and the iodination reaction of **1** readily proceeds under mild conditions.

In these cases, it turned out that an equimolar amount of $ZnCl_2$ was required for BTMA Br_3 or BTMA ICl_2. We, thus, assumed the existence of complexes formed from the polyhalides and $ZnCl_2$ as active species, and proposed that a reaction scheme which affords **2** (mono-bromoarenes) or **3** (mono-iodoarenes) may be described according to the following equations:

$$PhCH_2(CH_3)_3N^+XY_2^- + ZnCl_2 \longrightarrow [PhCH_2(CH_3)_3N]^+[ZnCl_2Y_2]^{2-}X^+ \quad (1)$$

$$\underset{\mathbf{1}}{Ar\text{-}H} + [PhCH_2(CH_3)_3N]^+[ZnCl_2Y_2]^{2-}X^+ \longrightarrow \underset{\mathbf{2}\text{ or }\mathbf{3}}{Ar\text{-}X} + PhCH_2(CH_3)_3N^+Y^- + ZnCl_2 + HY. \quad (2)$$

That is, the reaction appeared to occur in accord with the following stoichiometry:

$$\underset{\mathbf{1}}{H\text{-}Ar} + PhCH_2(CH_3)_3N^+XY_2^- \xrightarrow{ZnCl_2} \underset{\mathbf{2}\text{ or }\mathbf{3}}{Ar\text{-}X} + PhCH_2(CH_3)_3N^+Y^- + HY. \quad (3)$$

$$\left(\begin{array}{l} X=Y=Br \text{ for BTMA } Br_3 \\ X=I,\ Y=Cl \text{ for BTMA } ICl_2 \end{array}\right)$$

Incidentally, we found that $ZnCl_2$ was a more effective Lewis acid catalyst than other $AlCl_3$, $AlBr_3$, $FeCl_3$, and $ZnBr_2$.

As shown in Table 1, the bromination of **1** using BTMA $Br_3/ZnCl_2$ proceeded more easily than the iodination of **1** using BTMA $ICl_2/ZnCl_2$. Avramoff et al. have already reported the bromination of **1** with tetramethylammonium tribromide (TMA Br_3) in acetic acid under reflux.[44)] However, TMA Br_3 is not easy to handle, compared with stable BTMA Br_3 due to its hygroscopic character. Unfortunately, by our method the bromination of benzene did not proceed

Table 1. Bromination and Iodination of **1** by Use of BTMA Br_3/$ZnCl_2$ and BTMA ICl_2/$ZnCl_2$ in AcOH

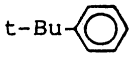
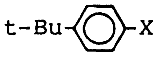
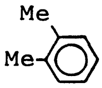
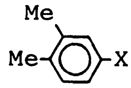
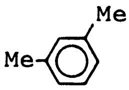
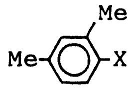
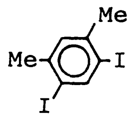
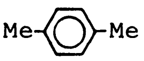
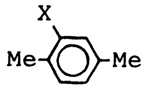
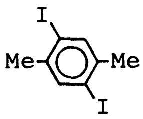
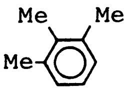
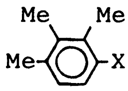
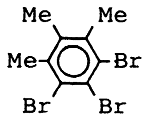
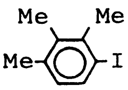
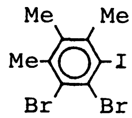
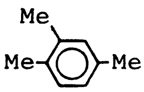
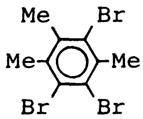
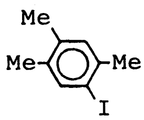
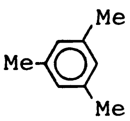
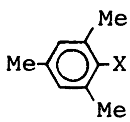
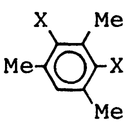
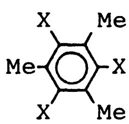
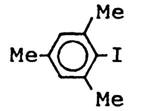
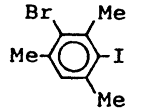
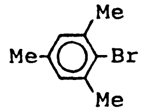
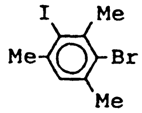
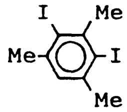
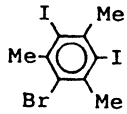
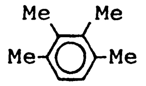
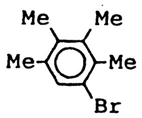
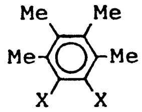
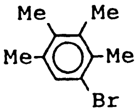
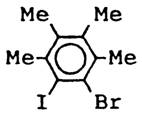
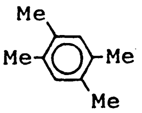
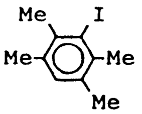
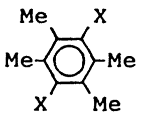
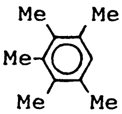
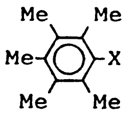
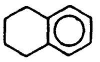
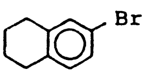
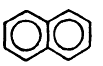
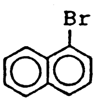
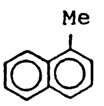
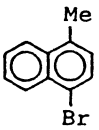
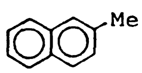
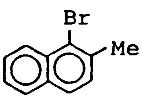
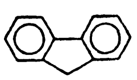
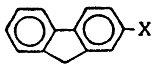
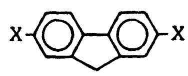
Substrate **1**	Molar ratio (BTMA Br_3/**1**, BTMA ICl_2/**1**)	Reaction conditions time/h	Reaction conditions temp/°C	Product (**2**: X=Br, **3**: X=I)		Yield[a)] %	Mp(°C) or Bp(°C/mmHg) Found	Mp(°C) or Bp(°C/mmHg) Reported
 (**1a**)	1.1	2	70		**2a-1**	95	228/760	228—229/740[14)]
	1.1	24	70		**3a-1**	92	258/760	116—118/9[15)]
 (**1b**)	1.1	2	rt		**2b-1**	69	215—216/760	214—215/760[16)]
	1.1	24	rt		**3b-1**	40	229/760	228—235/760[17)]
 (**1c**)	1.1	1	rt		**2c-1**	73	205.5—207/760	200—205/760[18)]
	1.1	24	rt		**3c-1**	66	233/760	232/760[19)]
1c	2.1	120	70		**3c-2**	60	66—68	72[17)]
 (**1d**)	1.0	2	rt		**2d-1**	84	203—204/760	205/760[20)]
	1.0	16	rt		**3d-1**	75	232—233/760	110—113/19[21)]
1d	2.1	72	70		**3d-2**	67	103—104	104—105[19)]
 (**1e**)	1.0	1	rt		**2e-1**	99	231/760	229.5/750[22)]
	1.0	43	rt		**3e-1**	90	270/760	144—145/22[23)]
1e	3.1	24	70[b)]		**2e-3**	99	241—242	246[24)]
 (**3e-1**)	2.1	78	70[b)]			93	223—224	—
 (**1f**)	3.1	24	70[b)]		**2f-3**	99	230—231	232[25)]
1f	1.0	48	rt		**3f-1**	97	36—37	36—37[23)]
 (**1g**)	1.1	6	reflux[c)]		**2g-1**	93	223/760	78—80[26)]
	1.0	3	rt		**3g-1**	90	30.5—31	30.5—31[27)]
1g	2.0	0.5	rt		**2g-2**	96	62—63	64[28)]
	2.0	28	70		**3g-2**	99	82	82[29)]
1g	3.1	24	70[b)]		**2g-3**	96	224	224—225[30)]
	3.1	120	70		**3g-3**	54	206—207	208[31)]

Table 1. (Continued)

Substrate 1	Molar ratio (BTMA Br_3/**1**, BTMA ICl_2/**1**)	Reaction conditions time/h	Reaction conditions temp/°C	Product (**2**: X=Br, **3**: X=I)		Yield[a)] %	Mp(°C) or Bp(°C/mmHg) Found	Mp(°C) or Bp(°C/mmHg) Reported
 (**3g-1**)	1.0	18	rt			77	42—43	—
 (**2g-1**)	1.0	24	70			87	42—43	—
 (**3g-2**)	1.1	78	70[b)]			87	184—185	—
 (**1h**)	1.0	2	rt		**2h-1**	96	30	29—30[32)]
1h	2.1	2	rt		**2h-2**	85	209—210	208[32)]
	2.1	24	70		**3h-2**	88	189—190	191—192[33)]
 (**2h-1**)	1.1	24	70			93	188	190—191[33)]
 (**1i**)	1.0	24	rt		**3i-1**	90	78	78—80[34)]
1i	2.1	3	rt		**2i-2**	90	202—203	200[32)]
	2.1	48	70		**3i-2**	76	138—139	140—141[33)]
 (**1j**)	1.1	2	rt		**2j-1**	95	163.5—164.5	159—160[35)]
	1.1	6	rt		**3j-1**	99	140	141—142[34)]
 (**1k**)	1.0	1	rt		**2k-1**	93	241/760	238—239/760[36)]
 (**1l**)	1.0	3	rt		**2l-1**	96	272/760	272—273/740[37)]
 (**1m**)	1.0	3	rt		**2m-1**	99	298—300/760	140—142/8[38)]
 (**1n**)	1.0	0.5	rt		**2n-1**	99	290—292/760	154—154.5/13[39)]
 (**1o**)	1.0	0.5	rt		**2o-1**	99	102—103	101—102[40)]
	1.0	3	rt		**3o-1**	94	124—125	126—127[41)]
1o	2.1	6	rt		**2o-2**	97	165—166	166.5—167[42)]
	2.1	3	70		**3o-2**	95	214—215	155.5[43)]

a) Yield of isolated product. b) Reaction was carried out by shading the light in order to prevent a side chain bromination. c) 1,2-Dichloroethane-methanol was used as solvent instead of acetic acid contained $ZnCl_2$.

and the bromination of toluene gave a mixture of *o*-, *p*-bromo and dibromo derivatives.

The reaction of **1** with equimolar amount of BTMA ICl_2 and $ZnCl_2$ at room temperature usually gave monoiodoarenes, and with 2-equiv of BTMA ICl_2 and $ZnCl_2$ at 70 °C usually gave diiodoarenes. Thus, the objective mono-, or diiodoarenes could be obtained selectively from **1** by the use of a calculated amount of BTMA ICl_2 and $ZnCl_2$ in acetic acid. However, by our method the iodination of less reactive benzene hardly proceeded; otherwise, the iodination of monoalkylbenzenes, such as toluene and ethylbenzene, gave a mixture of *o*-, *p*-iodo and diiodo derivatives, respectively, with nonselective manners. In the case of *t*-butylbenzene (**1a**), only a *p*-iodo compound **3a-1** was obtained, owing to a steric hindrance of the large *t*-butyl moiety.

Keefer et al. have reported the iodination of **1** such as 1,3,5-trimethylbenzene (**1g**) and 1,2,3,4,5-pentamethylbenzene (**1j**) by the use of ICl and $ZnCl_2$ in acetic acid.[27] However, it takes a long time to obtain the iodo compound, compared with our iodination method. Furthermore, ICl is not easy to handle quantitatively because of its viscous character.

Experimental

All melting points are uncorrected. The ^{1}H NMR spectra were recorded on a JMN-MH-100 spectrometer with tetramethylsilane as an internal standard.

Benzyltrimethylammonium Tribromide (BTMA Br_3). A partially improved preparative method is as follows: Benzyltrimethylammonium chloride (9.3 g, 50 mmol) and sodium bromate (3.8 g, 25 mmol) was dissolved in water (80 ml); dichloromethane (50 ml) was then added to the aqueous solution. To an ice-cold mixture of the above-mentioned solution was added dropwise 47% hydrobromic acid (30.2 g, 175 mmol) under stirring over a period of 15 min. The dichloromethane layer (dark red) was separated and the water layer was extracted with dichloromethane (20 ml×3). The combined organic solution was dried over magnesium sulfate and evaporated in vacuo to give a residue which was recrystallized from dichloromethane–ether (5 : 1) affording BTMA Br_3 as orange crystals; yield 16.6 g (85%); mp 100—101 °C (lit,[45] mp 100—101 °C).

2,5-Dimethyl-1-bromobenzene (2d-1). Typical Procedure of Bromination at Room Temperature: To a solution of 1,4-dimethylbenzene (**1d**) (0.50 g, 4.71 mmol) in acetic acid (30 ml) was added BTMA Br_3 (1.84 g, 4.71 mmol) and $ZnCl_2$ (0.7 g, 5.13 mmol). The mixture was stirred for 2 h at room temperature until the initial orange color faded. To the mixture was added water (20 ml) and 5% aq. solution of $NaHSO_3$ (10 ml). The mixture was extracted with hexane (40 ml×4). The organic layer was dried over magnesium sulfate and passed through a short alumina-column. The elute (hexane solution) was concentrated in vacuo to give **2d-1** as colorless oil; yield 0.74 g (84%); bp 203—204 °C/760 mmHg (lit,[20] bp 205 °C/760 mmHg; 1 mmHg≈133.322 Pa).

1-Bromo-4-*t*-butylbenzene (2a-1). Typical Procedure of Bromination at 70 °C. To a solution of *t*-butylbenzene (**1a**) (0.50 g, 3.73 mmol) in acetic acid (20 ml) was added BTMA Br_3 (1.60 g, 4.10 mmol) and $ZnCl_2$ (0.7 g, 5.13 mmol). The mixture was stirred for 2 h at 70 °C until the initial orange color faded. A subsequent work-up as mentioned above gave **2a-1** as colorless oil; yield 0.75 g (95%); bp 228 °C/760 mmHg (lit,[14] bp 228—229 °C/740 mmHg).

1-Iodo-2,4,6-trimethylbenzene (3g-1). Typical Procedure of Iodination: To a solution of 1,3,5-trimethylbenzene (**1g**) (0.50 g, 4.16 mmol) in acetic acid (20 ml) was added BTMA ICl_2 (1.45 g, 4.17 mmol) and $ZnCl_2$ (0.6 g, 4.40 mmol). The mixture was stirred for 3 h at room temperature. The yellow color of the solution gradually changed to light brown. To the mixture was added water (20 ml) and 5% aq. solution of $NaHSO_3$ (10 ml). Then, the mixture was extracted with hexane (50 ml×3). The organic layer was dried over $MgSO_4$ and passed through a short alumina-column in order to remove any trace amount of acetic acid. The hexane solution was concentrated in vacuo to give **3g-1** as colorless crystals; yield 0.92 g (90%); mp 30.5—31 °C (lit,[27] mp 30.5—31 °C).

1,2-Dibromo-3-iodo-4,5,6-trimethylbenzene: This compound was obtained as colorless crystals; mp 223—224 °C (from ethanol). ^{1}H NMR ($CDCl_3$) δ=2.30, 2.45, and 2.58 (9H, three s, three CH_3). Found: C, 27.00; H, 2.05%. Calcd for $C_9H_9IBr_2$: C, 26.77; H, 2.25%.

1-Bromo-3-iodo-2,4,6-trimethylbenzene: Mp 42—43 °C (from ethanol–water (1 : 3)). ^{1}H NMR ($CDCl_3$) δ=2.30, 2.35, and 2.70 (9H, three s, three CH_3), and 6.88 (1H, s, 5-H). Found: C, 33.27; H, 3.01%. Calcd for $C_9H_{10}IBr$: C, 33.26; H, 3.10%.

1-Bromo-3,5-diiodo-2,4,6-trimethylbenzene: This compound was obtained as colorless crystals; mp 184—185 °C (from ethanol). ^{1}H NMR ($CDCl_3$) δ=2.77 (6H, s, 2- and 6-CH_3), and 2.93 (3H, s, 4-CH_3). Found: C, 24.25; H, 2.01%. Calcd for $C_9H_9I_2Br$: C, 23.98; H, 2.01%.

2,7-Diiodofluorene (3o-2): Mp 214—215 °C (from ethanol–water (1 : 1)). (lit,[43] mp 155.5 °C). ^{1}H NMR ($CDCl_3$) δ=3.80 (2H, s, CH_2) and 7.4—8.0 (6H, m, Harom). Found: C, 37.29; H, 1.87%. Calcd for $C_{13}H_8I_2$: C, 37.35; H, 1.93%.

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