Halogenation using Quaternary Ammonium Polyhalides. Part 22.[1] Selective Bromination of Aromatic Ethers with Benzyltrimethylammonium Tribromide

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The reaction of aromatic ethers with a stoicheiometric amount of benzyltrimethylammonium tribromide in dichloromethane–methanol or acetic acid–$ZnCl_2$ under mild conditions gave, selectively, mono-, di-, or tri-bromo-substituted aromatic ethers in quantitative yields.

Bromo-substituted aromatic ethers have occasionally been prepared by the direct electrophilic aromatic substitution of aromatic ethers with molecular bromine in an appropriate solvent such as acetic acid[2] or carbon tetrachloride.[3] *O*-Alkylation of bromophenols has been used for the preparation of bromoaromatic ethers.[4] The Sandmeyer method for alkoxy-substituted aromatic amines has also been used to obtain pure bromo-aromatic ethers.[5] *N*-Bromosuccinimide (NBS) has also been employed occasionally.[6]

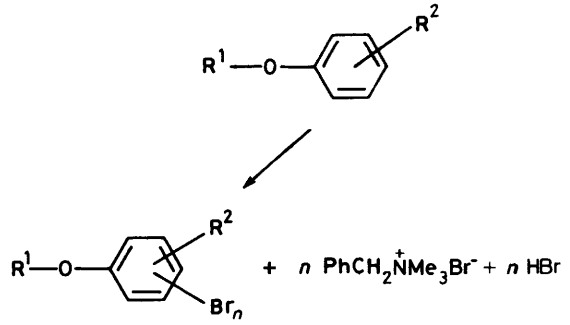
We have shown that benzyltrimethylammonium tribromide ($BTMA\cdot Br_3$) is a useful stable reagent for brominating aromatic compounds such as phenols,[7] aromatic amines,[8] and acetanilides.[9] Our preliminary work demonstrated that $BTMA\cdot Br_3$ in dichloromethane–methanol acts as an effective brominating agent for several aromatic ethers.[10] We now report the selective bromination of a wide range of aromatic ethers by use of $BTMA\cdot Br_3$ in dichloromethane–methanol or in acetic acid in the presence of $ZnCl_2$.

Results and Discussion

The reaction of aromatic ethers with a stoicheiometric amount of $BTMA\cdot Br_3$ in dichloromethane–methanol or in acetic acid–$ZnCl_2$ gave, selectively, the desired mono-, di-, or tri-bromo-substituted aromatic ethers in quantitative yields. For example, the reaction of 1-methoxy-3,5-dimethylbenzene with 1.0 equiv. of $BTMA\cdot Br_3$ in dichloromethane–methanol at room temperature gave 4-bromo-1-methoxy-3,5-dimethylbenzene, and that with 2.0 equiv. of $BTMA\cdot Br_3$ and $ZnCl_2$ in acetic acid at room temperature gave 2,4-dibromo-1-methoxy-3,5-dimethylbenzene; further, the reaction with 3.0 equiv. of $BTMA\cdot Br_3$ and $ZnCl_2$ in acetic acid at 70 °C gave 2,4,6-tribromo-1-methoxy-3,5-dimethylbenzene, in good yields. The results are summarized in the Table.

We have already reported that the presence of methanol markedly facilitates the electrophilic bromination of aromatic compounds with $BTMA\cdot Br_3$ in dichloromethane, and suggested the formation of methyl hypobromite as the active species.[3,6] $BTMA\cdot Br_3$ is only slightly soluble in acetic acid at room temperature, but the addition of $ZnCl_2$ increases its solubility, allowing the bromination of aromatic ethers to proceed smoothly under mild conditions. An equimolar amount of $ZnCl_2$ with respect to $BTMA\cdot Br_3$ is required. We proposed the existence of the $[PhCH_2NMe_3]^+[ZnCl_2Br_2]^{2-}Br^+$ complex as the active species, formed from $BTMA\cdot Br_3$ and an equimolar amount of $ZnCl_2$.[3,7]

As shown in the Table, monobromo-substituted aromatic ethers can usually be obtained from aromatic ethers using



Reagents: $n\ PhCH_2\overset{+}{N}Me_3Br^-$ in CH_2Cl_2–MeOH or AcOH–$ZnCl_2$.

an equimolar amount of $BTMA\cdot Br_3$ in dichloromethane–methanol, and di- or tri-bromo-substituted products may be prepared by use of 2 or 3 equiv., respectively, of $BTMA\cdot Br_3$ and $ZnCl_2$ in acetic acid. In fact, the reaction of aromatic ethers (except active compounds such as 1,3-dimethoxybenzene, 1,3-diethoxybenzene, and 1,3,5-trimethoxybenzene) with $BTMA\cdot Br_3$ in dichloromethane–methanol gave only monobromo-substituted derivatives regardless of the presence of even a large excess of the reagent. In contrast, $BTMA\cdot Br_3$ in acetic acid–$ZnCl_2$ was so effective that this system could not be used to obtain monobromo-derivatives. Less reactive aromatic ethers such as 1-methoxy-2-nitro- and 1-methoxy-4-nitro-benzene were not brominated in dichloromethane–methanol, but their monobromo-derivatives could be obtained by using $BTMA\cdot Br_3$ in acetic acid–$ZnCl_2$ in quantative yields (see Table).

We believe that this procedure for the selective bromination of aromatic ethers should prove to be useful owing to its ease, mildness of conditions, and good yields.

Experimental

^1H NMR spectra were recorded on a JMN-MH-100 spectrometer with tetramethylsilane as internal standard. All m.p.s and b.p.s are uncorrected.

4-Bromo-1-methoxybenzene; Typical Procedure using $BTMA\cdot Br_3$ *and methanol* (*Table, entry* 1).—To a solution of methoxybenzene (0.50 g, 4.62 mmol) in dichloromethane (50 ml)–methanol (20 ml) was added $BTMA\cdot Br_3$[3,7] (1.98 g, 5.08 mmol). The mixture was stirred at room temperature for 2 h until the initial orange colour faded. The solvent was distilled off and water (20 ml) added to the residue. The mixture was extracted with ether (4 × 40 ml). The ethereal layer was dried

Table. Selective bromination of aromatic ethers with BTMA·Br_3.

Entry	Substrate	Molar ratio[a]	Reaction conditions: Temp./°C	Time	Solvent (additive)	Product[b] (yield,[c] %)
1	PhOMe	1.1	rt,[d]	2 h	CH_2Cl_2 (MeOH)	4-BrC_6H_4OMe[2] (98)
2	PhOMe	2.1	70	2 h	AcOH ($ZnCl_2$)	2,4-$Br_2C_6H_3OMe$[2] (97)
3	PhOEt	1.1	rt	1 h	CH_2Cl_2 (MeOH)	4-BrC_6H_4OEt[6] (98)
4	PhOEt	2.1	70	2 h	AcOH ($ZnCl_2$)	2,4-$Br_2C_6H_3OEt$[11] (98)
5	PhOBu	1.1	rt	1 h	CH_2Cl_2 (MeOH)	4-BrC_6H_4OBu[12] (98)
6	PhOBu	2.1	70	2 h	AcOH ($ZnCl_2$)	2,4-$Br_2C_6H_3OBu$ (98)
7	2-MeC_6H_4OMe	1.1	rt	30 min	CH_2Cl_2 (MeOH)	4-Br-2-MeC_6H_3OMe[13] (98)
8	2-MeC_6H_4OMe	2.1	rt	8 h	AcOH ($ZnCl_2$)	2,4-Br_2-6-MeC_6H_2OMe[14] (94)
9	3-MeC_6H_4OMe	1.1	rt	3 min	CH_2Cl_2 (MeOH)	4-Br-3-MeC_6H_3OMe[5] (98)
10	3-MeC_6H_4OMe	3.1	70	9 h	AcOH ($ZnCl_2$)	2,4,6-Br_3-3-MeC_6HOMe[15] (98)
11	4-MeC_6H_4OMe	1.0	rt	10 min	AcOH ($ZnCl_2$)	2-Br-4-MeC_6H_3OMe[4] (93)
12	2,3-$Me_2C_6H_3OMe$	1.1	rt	1 min	CH_2Cl_2 (MeOH)	4-Br-2,3-$Me_2C_6H_2OMe$[16] (98)
13	2,3-$Me_2C_6H_3OMe$	2.1	rt	2 h	AcOH ($ZnCl_2$)	4,6-Br_2-2,3-Me_2C_6HOMe (98)
14	2,4-$Me_2C_6H_3OMe$	1.1	rt	20 min	AcOH ($ZnCl_2$)	2-Br-4,6-$Me_2C_6H_2OMe$[17] (93)
15	2,5-$Me_2C_6H_3OMe$	1.1	rt	1 min	CH_2Cl_2 (MeOH)	4-Br-2,5-$Me_2C_6H_2OMe$ (98)
16	2,5-$Me_2C_6H_3OMe$	2.1	rt	2 h	AcOH ($ZnCl_2$)	2,4-Br_2-3,6-Me_2C_6HOMe[18] (97)
17	2,6-$Me_2C_6H_3OMe$	1.1	rt	20 min	AcOH ($ZnCl_2$)	4-Br-2,6-$Me_2C_6H_2OMe$[19] (98)
18	3,4-$Me_2C_6H_3OMe$	1.1	rt	5 min	CH_2Cl_2 (MeOH)	2-Br-4,5-$Me_2C_6H_2OMe$[20] (97)
19	3,4-$Me_2C_6H_3OMe$	2.1	rt	1 h	AcOH ($ZnCl_2$)	2,6-Br_2-3,4-Me_2C_6HOMe (95)
20	3,5-$Me_2C_6H_3OMe$	1.0	rt	1 min	CH_2Cl_2 (MeOH)	4-Br-3,5-$Me_2C_6H_2OMe$[3] (98)
21	3,5-$Me_2C_6H_3OMe$	2.0	rt	30 min	AcOH ($ZnCl_2$)	2,4-Br_2-3,5-Me_2C_6HOMe[21] (92)
22	3,5-$Me_2C_6H_3OMe$	3.0	70	2 h	AcOH ($ZnCl_2$)	2,4,6-Br_3-3,5-Me_2C_6OMe[22] (93)
23	1,2-$(MeO)_2C_6H_4$	1.1	rt	1 h	CH_2Cl_2 (MeOH)	4-$BrC_6H_3(OMe)_2$-1,2[23] (98)
24	1,2-$(MeO)_2C_6H_4$	2.1	rt	1 h	AcOH ($ZnCl_2$)	4,5-$Br_2C_6H_2(OMe)_2$-1,2[24] (97)
25	1,2-$(MeO)_2C_6H_4$	4.1	70	24 h	AcOH ($ZnCl_2$)	3,4,5,6-$Br_4C_6(OMe)_2$-1,2 (89)
26	1,3-$(MeO)_2C_6H_4$	2.1	rt	1 min	CH_2Cl_2 (MeOH)	2,4-$Br_2C_6H_2(OMe)_2$-1,5[25] (98)
27	1,3-$(MeO)_2C_6H_4$	3.1	70	15 h	AcOH ($ZnCl_2$)	2,4,6-$Br_3C_6H(OMe_2)$-1,3[26] (83)
28	2,4-$Br_2C_6H_2$-1,5-$(MeO)_2$	1.1	70	17 h	AcOH ($ZnCl_2$)	2,4,6-$Br_3C_6H(OMe_2)$-1,3[26] (89)
29	1,3-$(EtO)_2C_6H_4$	2.1	rt	1 min	CH_2Cl_2 (MeOH)	2,4-$Br_2C_6H_2(OEt)_2$-1,5[27] (98)
30	1,3-$(EtO)_2C_6H_4$	3.1	70	17 h	AcOH ($ZnCl_2$)	2,4,6-$Br_3C_6H(OEt)_2$-1,3[27] (85)
31	1,4-$(MeO)_2C_6H_4$	2.1	rt	3 h	AcOH ($ZnCl_2$)	2,5-$Br_2C_6H_2(OMe)_2$-1,4[28] (98)
32	1,4-$(MeO)_2C_6H_4$	4.1	70	24 h	AcOH ($ZnCl_2$)	2,3,5,6-$Br_4C_6(OMe)_2$-1,4[29] (86)
33	1,3,5-$(MeO)_3C_6H_3$	2.1	rt	1 min	CH_2Cl_2 (MeOH)	2,4-$Br_2C_6H(OMe)_3$-1,3,5[30] (98)
34	1,3,5-$(MeO)_3C_6H_3$	3.1	rt	2 h	AcOH ($ZnCl_2$)	2,4,6-$Br_2C_6(OMe)_3$-1,3,5[31] (96)
35	2-BrC_6H_2-1,3,5-$(MeO)_3$	2.1	rt	2 h	AcOH ($ZnCl_2$)	2,4,6-$Br_3C_6(OMe)_3$-1,3,5[31] (95)
36	2,4-Br_2C_6H-1,3,5-$(MeO)_3$	1.1	rt	2 h	AcOH ($ZnCl_2$)	2,4,6-$Br_3C_6(OMe)_3$-1,3,5[31] (95)
37	$(C_6H_5)_2O$	2.1	rt	20 min	AcOH ($ZnCl_2$)	$(4\text{-}BrC_6H_4)_2O$[32] (98)
38	$C_6H_5CH_2OC_6H_5$	1.1	rt	25 min	AcOH ($ZnCl_2$)	$PhCH_2OC_6H_4Br$-4[33] (98)
39	$(C_6H_5OCH_2)_2$	2.1	rt	2 h	CH_2Cl_2 (MeOH)	$(4\text{-}BrC_6H_4OCH_2)_2$[34] (98)
40	$(C_6H_5OCH_2)_2$	4.1	70	2 h	AcOH ($ZnCl_2$)	$(2,4\text{-}Br_2C_6H_3OCH_2)_2$ (98)
41	2-$NO_2C_6H_4OMe$	1.1	70	17 h	AcOH ($ZnCl_2$)	4-Br-2-$NO_2C_6H_3OMe$[35] (98)
42	4-$NO_2C_6H_4OMe$	1.1	70	17 h	AcOH ($ZnCl_2$)	2-Br-4-$NO_2C_6H_3OMe$[35] (97)

[a] BTMA·Br_3/substrate. [b] Known products were characterized by comparison with authentic material (^1H NMR and IR spectra, and b.p. or m.p.). [c] Yield of isolated product. [d] rt = room temperature.

over $MgSO_4$ and evaporated under reduced pressure to give 4-bromo-1-methoxybenzene as colourless oil; yield 0.84 g (98%); b.p. 213 °C at 760 mmHg (lit.,[2] b.p. 124 °C at 40 mmHg).

2,4-*Dibromo*-1-*methoxybenzene; Typical Procedure using* BTMA·Br_3 *with Zinc Chloride* (*Table, entry* 2).—To a solution of methoxybenzene (0.50 g, 4.62 mmol) in acetic acid (20 ml) was added BTMA·Br_3 (3.79 g, 9.72 mmol) and $ZnCl_2$ (1.5 g, 11.0 mmol). The mixture was stirred for 2 h at 70 °C until the orange colour faded. To the mixture was added water (20 ml) and 5% aqueous $NaHSO_3$ (10 ml). The mixture was extracted with hexane (4 × 40 ml). The organic layer was dried over $MgSO_4$, and passed through a short column of alumina. The eluate (hexane solution) was concentrated under reduced pressure to give 2,4-dibromo-1-methoxybenzene as colourless crystals; yield 1.19 g (97%); m.p. 60–61 °C (lit.,[2] m.p. 61–62 °C).

Characterization of New Compounds.—2,4-*Dibromo*-1-*butoxybenzene* (entry 6) was a colourless oil, b.p. 300–302 °C at 760 mmHg; ^1H NMR ($CDCl_3$): δ 0.78–2.05 (m, 7 H, Pr), 3.85 (t, *J* 6 Hz, 2 H, CH_2O), and 6.48–7.52 (m, 3 H, ArH) (Found: C, 38.9; H, 3.75%. $C_{10}H_{12}Br_2O$ requires C, 39.0; H, 3.9%).

4,6-*Dibromo*-1-*methoxy*-2,3-*dimethylbenzene* (entry 13) formed colourless crystals [from ethanol–water (1:3)], m.p. 21 °C; ^1H NMR ($CDCl_3$): δ 2.27 (s, 6 H, 2- and 3-Me), 3.72 (s, 3 H, OMe), and 7.52 (s, 1 H, 5-H) (Found: C, 36.3; H, 3.3. $C_9H_{10}Br_2O$ requires C, 36.8; H, 3.4%).

4-*Bromo*-1-*methoxy*-2,5-*dimethylbenzene* (entry 15) formed colourless crystals [from ethanol–water (1:3)], m.p. 28–29 °C; ^1H NMR ($CDCl_3$): δ 2.11 (s, 3 H, 2-Me), 2.27 (s, 3 H, 5-Me), 3.65 (s, 3 H, OMe), 6.51 (s, 1 H, 6-H), and 7.10 (s, 1 H, 3-H) (Found: C, 50.0; H, 5.2. $C_9H_{11}BrO$ requires C, 50.3; H, 5.2%).

2,6-*Dibromo*-1-*methoxy*-3,4-*dimethylbenzene* (entry 19) formed colourless crystals [from ethanol–water (1:3)], m.p. 55–56 °C; ^1H NMR ($CDCl_3$): δ 2.18 (s, 3 H, 4-Me), 2.20 (s, 3 H, 3-Me), 3.75 (s, 3 H, OMe), and 7.07 (s, 1 H, 5-H) (Found: C, 36.6; H, 3.4. $C_9H_{10}Br_2O$ requires C, 36.8; H, 3.4%).

3,4,5,6-*Tetrabromo*-1,2-*dimethoxybenzene* (entry 25) formed colourless crystals (from methanol), m.p. 127–127.5 °C; ^1H

NMR ($CDCl_3$): δ 3.88 (s, 6 H, 2 × OMe) (Found: C, 21.2; H, 1.3. $C_8H_6Br_4O_2$ requires C, 21.2; H, 1.3%).

1,2-*Bis*(2,4-*dibromophenoxy*)*ethane* (entry 40) formed colourless crystals (from methanol), m.p. 179–180 °C; ^1H NMR ($CDCl_3$): δ 4.39 (s, 4 H, 2 × OCH_2) and 6.7–7.7 (m, 6 H, ArH) (Found: C, 31.8; H, 1.9. $C_{14}H_{10}Br_4O_2$ requires C, 31.7; H, 1.9%).

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