CHEMISTRY LETTERS, pp. 415-418, 1989.

Facile Synthesis of Chloro-substituted Aromatic Ethers by Use of Benzyltrimethylammonium Tetrachloroiodate[1)]

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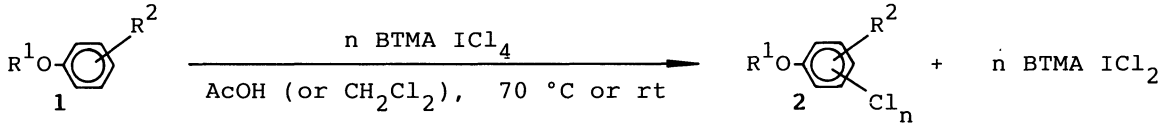
The reaction of aromatic ethers with a calculated amount of benzyltrimethylammonium tetrachloroiodate in acetic acid (or dichloromethane) under mild conditions gave, selectively, the objective chloro-substituted aromatic ethers in good yields.

For the chlorination of aromatic ethers (**1**), various reagents have been used in place of toxic gaseous chlorine. For example, alkyl hypochlorites (t-butyl and methyl hypochlorites) in nitromethane,[2)] sulfuryl chloride catalyzed with diphenyl sulfide and aluminium chloride,[3)] and benzeneseleninyl chloride in the presence of aluminium chloride[4)] have been employed as regioselective chlorinating agents for anisole or phenetole. Methylated cyclodextrin and cyclodextrin polymer are available as effective catalyst for the selective anisole chlorination.[5)] Hexachlorocyclohexadienones have also chlorinated anisole predominantly in the para position.[6)] Furthermore, N-chloramine derivatives such as N-chlorotriethylammonium chloride and N-chloropiperidine are used as site-selective monochlorinating agents for **1**.[7)] Chlorination of **1** by using titanium (IV) chloride has been carried out in the presence of oxidizing reagent peroxytrifluoroacetic acid.[8)] Anisole has been chlorinated with a sequence of chlorinating agents generated by the reaction of 4-substituted N-chloroacylanilides with appropriate carboxylic acids.[9)] However, many of these reagents are unstable, and must be freshly prepared just before their use.

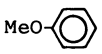
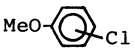
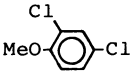
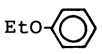
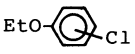
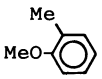
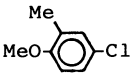
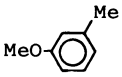
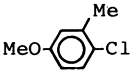
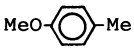
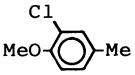
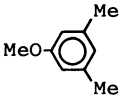
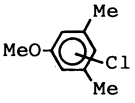
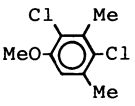
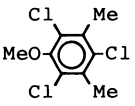
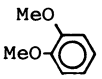
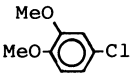
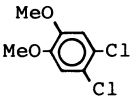
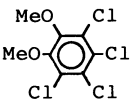
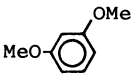
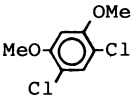
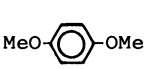
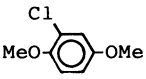
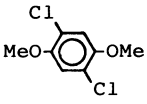
As a part of the investigation on the halogenation of aromatic compounds by use of quaternary ammonium polyhalides, we found that a new reagent benzyltrimethylammonium tetrachloroiodate (BTMA ICl_4) was an effective chlorinating agent. In this paper, we wish to report on a chlorination of **1** by the use of BTMA ICl_4.

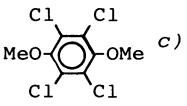
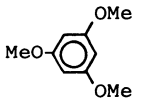
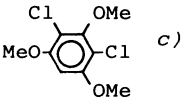
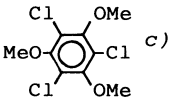
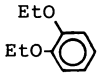
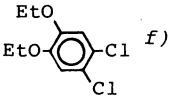
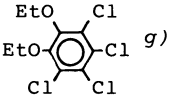
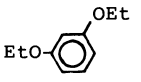
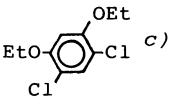
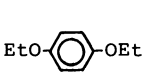
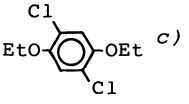
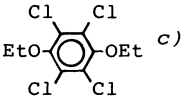
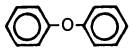
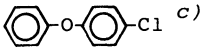
BTMA ICl_4, a yellow crystalline solid which is quite stable on storage at room temperature, can be easily prepared by bubbling chlorine gas into a mixture of benzyltrimethylammonium chloride (1 mol) and iodine (1/2 mol) in dichloromethane.[10)] The reaction of **1** with BTMA ICl_4 in acetic acid (or dichloromethane) at 70 °C or at room temperature gave chloro-substituted aromatic ethers (**2**)



together with benzyltrimethylammonium dichloroiodate (BTMA ICl_2). It is easy to separate BTMA ICl_2 from the reaction mixture since this polyhalide precipitates readily because of its poor solubility in these solvents. The results are summarized in Table 1.

Table 1. Chlorination of Aromatic Ethers (1) with BTMA ICl_4

Substrate (1)	Molar ratio BTMA ICl_4/1	Solvent	Reaction conditions temp/°C	time/h	Product (2)	Yield[a] %	Mp(°C) or Bp(°C/mmHg)
 (1a)	1.0	AcOH	70	24	 [b] (2a)	73	195-197/760
1a	2.0	AcOH	70	24	 [c] (2a-2)	90	226/760
 (1b)	1.0	AcOH	70	24	 [d] (2b)	96	90-92/11
 (1c)	1.0	AcOH	70	20	 [c] (2c-1)	75	210-212/760
 (1d)	1.0	AcOH	70	20	 [c] (2d-1)	74	215-216/760
 (1e)	1.0	AcOH	70	20	 [c] (2e-1)	73	213-215/760
 (1f)	1.0	AcOH	rt	20	 [e] (2f)	74	230-231/760
1f	2.0	AcOH	rt	20	 [c] (2f-2)	79	77-78
1f	3.0	AcOH	rt	20	 [c] (2f-3)	75	100
 (1g)	1.0	CH_2Cl_2	rt	20	 [c] (2g-1)	73	236-237/760
1g	2.0	AcOH	rt	1	 [c] (2g-2)	96	118-119
1g	4.0	AcOH	70	24	 [c] (2g-4)	90	90
 (1h)	2.0	AcOH	rt	1	 [c] (2h-2)	72	118-119
 (1i)	1.0	CH_2Cl_2	rt	20	 [c] (2i-1)	65	234-235/760
1i	2.0	AcOH	rt	1	 [c] (2i-2)	90	129-130

1i		4.0	AcOH	70	24	 *c)*	(**2i-4**)	71	163
	(**1j**)	2.0	AcOH	rt	1	 *c)*	(**2j-2**)	92	127
1j		3.0	AcOH	rt	1	 *c)*	(**2j-3**)	81	132
	(**1k**)	2.0	AcOH	rt	1	 *f)*	(**2k-2**)	93	275-276/760
1k		4.0	AcOH	70	24	 *g)*	(**2k-4**)	87	89
	(**1l**)	2.0	AcOH	rt	1	 *c)*	(**2l-2**)	92	89-90
	(**1m**)	2.0	AcOH	rt	1	 *c)*	(**2m-2**)	93	117-118
1m		4.0	AcOH	70	24	 *c)*	(**2m-4**)	87	106-107
	(**1n**)	1.0	AcOH	rt	24	 *c)*	(**2n-1**)	92	281/760

a) Yield of isolated product. *b)* Isomer ratio was determined by GC analysis and ^{1}H NMR spectrum: 4-chloro deriv. / 2-chloro deriv. = 6/1. *c)* Known products were characterized by comparing their ^{1}H NMR spectra and bp or mp with those of authentic samples or reported data. *d)* 4-chloro deriv. / 2-chloro deriv. = 3/1. *e)* 4-chloro deriv. / 2-chloro deriv. = 5/1. *f)* **2k-2**: ^{1}H NMR ($CDCl_3$) δ= 1.44 (6H, t, J= 8 Hz, $2C\underline{H}_3CH_2$), 4.04 (4H, q, J= 8 Hz, $2CH_3C\underline{H}_2$), 6.84 (2H, s, 3 and 6-H). Found: C, 51.32; H, 5.15%. Calcd for $C_{10}H_{12}O_2Cl_2$: C, 51.09; H, 5.14%. *g)* **2k-4**: ^{1}H NMR ($CDCl_3$) δ= 1.48 (6H, t, J= 8 Hz, $2C\underline{H}_3CH_2$), 4.28 (4H, q, J= 8 Hz, $2CH_3C\underline{H}_2$). Found: C, 39.51; H, 3.32%. Calcd for $C_{10}H_{10}O_2Cl_4$: C, 39.41; H, 3.23%.

As shown in Table 1, monochloro-substituted aromatic ethers can be obtained from **1** using an equimolar amount of BTMA ICl_4. Di-, tri-, or tetrachloro-substituted aromatic ethers have been obtained by the use of corresponding amounts of BTMA ICl_4. Accordingly, we can selectively prepare the desired polychloro-substituted **2** by using calculated amounts of BTMA ICl_4.

BTMA ICl_4 has a melting point of 106-125 °C. That is, this polyhalide sintered at 106-107 °C and melted completely at 125 °C. During the course of this heating step, BTMA ICl_4 decomposes in the following manner with an evolution of chlorine gas;

$$PhCH_2(CH_3)_3N^+ICl_4^- \xrightarrow{\Delta} Cl_2 + PhCH_2(CH_3)_3N^+ICl_2^-$$

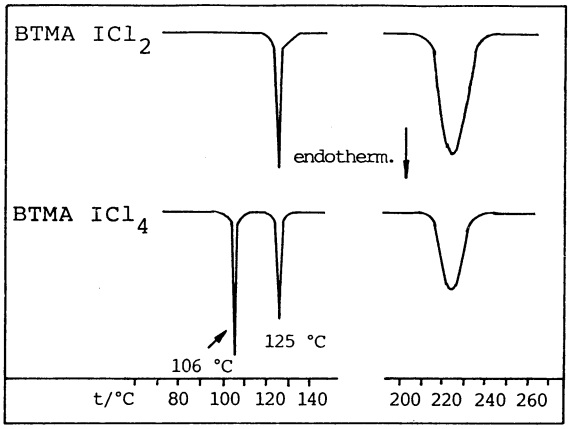


Fig.1. DTA Thermograms of BTMA ICl_4 and BTMA ICl_2 at 5 °C/min.

Incidentally, BTMA ICl_2 shows its melting point at 125-126 °C.[11] DTA thermograms of BTMA ICl_4 and BTMA ICl_2 are shown in Fig. 1. Thus, BTMA ICl_4 is a crystalline substance which liberates one molar chlorine molecule upon heating. This stable reagent has a large merit in that it can be treated more safely and quantitatively as compared with toxic gaseous chlorine. By-product BTMA ICl_2 can be easily converted to BTMA ICl_4 by treatment with chlorine in dichloromethane.

One limitation of this method lies in that attempts for monochlorination of monoalkoxybenzene such as **1a** or **1b** give a mixture of 2-, 4-chloro, and 2,4-dichloro-substituted products. Furthermore, chlorinations of nitroanisoles(less reactive than **1**a-f) are unsuccessful.

Monochlorination of anisole(**1a**); the typical procedure: To a solution of anisole(**1a**)(5.0 g, 46 mmol) in AcOH(100 ml) was added BTMA ICl_4(19.3 g, 46 mmol), and the mixture was stirred for 24 h at 70 °C. A yellow color of the solution gradually changed to reddish brown, and a yellow precipitate was deposited. After cooling the precipitate(BTMA ICl_2, 15.3 g, 44 mmol) was filtered off. The filtrate was treated with 5% $NaHSO_3$(200 ml) and extracted with benzene(40 ml x 3). The benzene extract was washed with 5% $NaHCO_3$(150 ml) and then purified by column chromatography on alumina. The eluent was concentrated in vacuo to give an oily residue(yield 6.0 g), which was confirmed by its ^1H NMR spectrum to be a 69 : 11 : 20 mixture of 4-, 2-, and 2,4-dichloroanisole. The oil was distilled to give a mixture of 4- and 2-chloroanisole (6 : 1) as a colorless liquid; 4.8 g (73%); bp 195-197 °C/760 mmHg.

References

1) Halogenation Using Quaternary Ammonium Polyhalides XVIII.
2) V. L. Heasley, G. E. Heasley, D. M. Ingel, D. D. Davis, and T. L. Rold, J. Org. Chem., 38, 2549 (1973).
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(Received November 30, 1988)