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Halogenation Using Quaternary Ammonium Polyhalides. XXXI[1]
Halogenation of Thiophene Derivatives with Benzyltrimethylammonium Polyhalides

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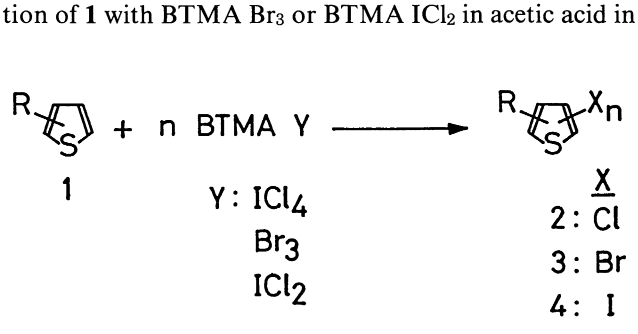
Synopsis. The reactions of thiophene derivatives with benzyltrimethylammonium tetrachloroiodate, benzyltrimethylammonium tribromide, and benzyltrimethylammonium dichloroiodate in acetic acid or in acetic acid–zinc chloride under mild conditions gave chloro-, bromo-, and iodo-substituted thiophene derivatives, respectively, in satisfactory yields.

Since thiophene derivatives (**1**) are sensitive toward the electrophilic substitution reactions, the halogenation of **1** generally gives a mixture of mono-, di-, and other polysubstituted halogenation products. For example, direct chlorination of thiophene (**1a**) with chlorine gave a mixture of 2-chloro-, 2,5-dichloro-, 2,3,4-trichloro-, 2,3,5-trichloro-, and 2,3,4,5-tetrachlorothiophene.[2] Bromination of **1a** with an equimolar amount of bromine gave 2-bromothiophene accompanying 2,5-dibromo- and a smaller amount of tribromothiophene as by-products.[3] Only 2-iodo- and 2,5-diiodothiophene can be synthesized by direct iodination of **1a** with iodine in the presence of mercury(II) oxide,[4] and other iodothiophenes can be prepared indirectly by the reaction of acetoxymercurio derivative with iodine.[5] Direct halogenation of 2-methylthiophene (**1b**) with chlorine[6] and bromine,[7] also gave the mixtures, respectively. By the iodination of **1b** with iodine–mercury(II) oxide, 5-iodo derivative is obtained,[8] and other iodo derivatives have been synthesized by indirect methods.

We have recently shown that benzyltrimethylammonium polyhalides such as benzyltrimethylammonium tetrachloroiodate (BTMA ICl_4),[9] benzyltrimethylammonium tribromide (BTMA Br_3),[10] and benzyltrimethylammonium dichloroiodate (BTMA ICl_2)[11] are useful aromatic chlorinating, brominating, and iodinating agents. In this paper we wish to report on the direct selective halogenation of aromatic heterocyclic compounds, especially **1**, with BTMA ICl_4, BTMA Br_3, and BTMA ICl_2.

Results and Discussion

The reaction of **1** with BTMA ICl_4 in acetic acid gave chloro-substituted thiophene derivatives (**2**). The reaction of **1** with BTMA Br_3 or BTMA ICl_2 in acetic acid in the presence of zinc chloride gave bromo- (**3**) or iodo-substituted thiophene derivatives (**4**), respectively. The results are summarized in Table 1.



As shown in the Table 1, these reactions usually proceeded stoichiometrically. However, in many cases, the reaction of **1** with BTMA ICl_4 gave a mixture of several chloro-substituted thiophene derivatives **2**, which could not be separated from each other.

In the cases of bromination and iodination, used zinc chloride may form complexes with BTMA Br_3 and BTMA ICl_2, producing such active species as $[PhCH_2(CH_3)_3N]^+[ZnCl_2Br_2]^{2-}Br^+$ and $[PhCH_2(CH_3)_3N]^+[ZnCl_4]^{2-}I^+$, respectively.[27]

We believe that the procedure for the direct halogenation of **1** using benzyltrimethylammonium polyhalides (stable solid reagents) is more useful and effective than that using molecular chlorine, bromine, or iodine, because of ease, simplicity and generality. As a limitation to the procedure, attempts at the monochlorination of **1** using an equimolar amount of BTMA ICl_4 were unsuccessful due to contamination of the polychlorinated products.

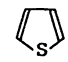
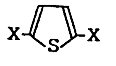
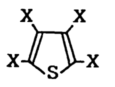
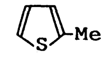
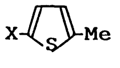
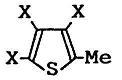
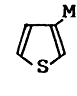
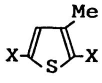
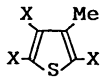
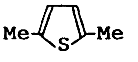
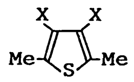
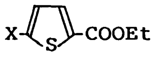
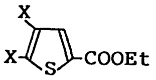
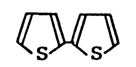
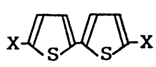
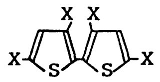
Experimental

3-Methyl-2,4,5-trichlorothiophene (2c-3); Typical Procedure for the Chlorination: BTMA ICl_4 (6.50 g, 15.5 mmol) was added to a solution of 3-methylthiophene (**1c**) (0.49 g, 5 mmol) in acetic acid (50 ml); the mixture was stirred at 70 °C for 24 h. During this time, the color of the solution turned black, and a yellow precipitate was deposited. After the solution was cooled to room temperature, the yellow precipitate (BTMA ICl_2) was filtered off. The filtrate was concentrated in vacuo and the obtained residue was treated with 5% $NaHSO_3$ (10 ml) and with 5% $NaHCO_3$ (10 ml), and then extracted with dichloromethane (50 ml×3). The black organic layer was separated and dried over $MgSO_4$. Then, a trace amount of acetic acid and black impurities in the solution were removed by column chromatography on alumina. The eluent was concentrated in vacuo to give a colorless oil **2c-3**; yield 0.64g (63%); bp 219 °C/760 mmHg (lit,[20] bp 115—116 °C/23 mmHg, 1 mmHg=133.322 Pa).

3,5,3′,5′-Tetrachloro-2,2′-dithienyl (2f-4): Mp 120—121 °C; ^1H NMR ($CDCl_3$) δ=6.77 (2H, s, 4- and 4′-H). Found: C, 31.42; H, 0.72%. Calcd for $C_8H_2S_2Cl_4$: C, 31.60; H, 0.66%.

2,5-Dibromothiophene (3a-2); Typical Procedure for the Bromination: BTMA Br_3 (3.90 g, 10 mmol) and $ZnCl_2$ (ca. 1 g) were added to a solution of thiophene (**1a**) (0.42 g, 5 mmol) in acetic acid (30 ml); the mixture was then stirred at room temperature for 2 h until the disappearance of the orange color of the reagent. Aqueous $NaHSO_3$ (5%, 10 ml) was added to the mixture; this mixture was extracted with hexane (50 ml×3). The organic layer was dried over $MgSO_4$, and passed through a short alumina-column. The eluent was concentrated in vacuo to give **3a-2** as a colorless oil; yield 0.65 g

Table 1. Halogenation of Thiophene Derivatives **1** with Benzyltrimethylammonium Polyhalides in AcOH

Substrate		Molar ratio	Reaction conditions[a)]		Product[b)]		Yield[c)]	Mp(°C) or Bp(°C/mmHg)	
1		Reagent/**1**	Temp/°C	Time/h	**2,3,4**		%	Found	Reported
	**1a**	2.0	70	49		—d)		—	—
			rt	2		**3a—2**	54	217—218/760	68/2[12)]
			rt	22		**4a—2**	41	42—43	41[13)]
		4.1	70	24		**2a—4**	33	225.5/760	233.4/760[14)]
			70	5		**3a—4**	72	106—107	117[15)]
			70	21		**4a—4**	39	202—204	199—200[16)]
	**1b**	1.0	rt	4		—d)		—	—
			rt	27		—e)		—	—
			rt	4		**4b—1**	42	oil	88.8—89/14[17)]
		3.1	70	23		—d)		—	—
			rt	15		**3b—3**	55	81.5—82.5	91[7)]
			70	24		—f)		—	—
	**1c**	2.0	rt	24		**2c—2**	81	185.3/760	65/11[18)]
			rt	15		**3c—2**	97	226—227/760	226—230/760[19)]
			rt	4		**4c—2**	92	238—240/760	120—121/2.5[20)]
		3.1	70	24		**2c—3**	63	219/760	115—116/23[21)]
			rt	15		**3c—3**	72	27—28.5	33[19)]
			rt	15		**4c—3**	94	73—74	75-76[20)]
	**1d**	2.1	70	24		—d)		—	—
			rt	20		**3d—2**	50	223—224/760	44—45[22)]
			rt	28		**4d—2**	98	80.5—81.5	83[19)]
	**1e**	1.0	rt	22		—d)		—	—
			rt	17		**3e—1**	86	174—175/760	113—114/6[23)]
			70	19		—f)		—	—
		3.1	70	24		—d)		—	—
			70	25		**3e—2**	55	48—49	—
			70	24		**4e—2**	77	96—97	—
	**1f**	2.1	rt	24		—d)		—	—
			rt	27		**3f—2**	99	145—146	146—147[24)]
			rt	15		**4f—2**	60	163—165	167—168[25)]
		4.1	70	24		**2f—4**	48	120—121	—
			70	26		**3f—4**	95	132—133	139—140[26)]
			70	19		—f)		—	—

a) In the cases of both bromination and iodination, $ZnCl_2$ was used as catalyst. b) Known products were characterized by comparing their ^1H NMR spectra and bp or mp with those of authentic samples or reported data. c) Yield of isolated product. d) Mixture of several chloro-substituted products. e) Mixtrue of several bromo-substituted products. f) Mixture of several iodo-substituted products.

(54%); bp 217—218 °C/760 mmHg (lit,[12)] bp 68 °C/2 mmHg).

Ethyl 4,5-Dibromo-2-thiophenecarboxylate (3e-2): Mp 55 °C; ^1H NMR ($CDCl_3$) δ=1.47 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.17 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), and 7.64 (1H, s, 3-H). Found: C, 26.50; H, 1.81%. Calcd for $C_7H_6O_2SBr_2$: C, 26.78; H, 1.93%.

2,5-Diiodo-3-methylthiophene (4c-2); Typical Procedure for the Iodination: BTMA ICl_2 (3.65 g, 10 mmol) and $ZnCl_2$ (ca. 1.5 g) were added to a solution of **1c** (0.49 g, 5 mmol) in acetic acid (30 ml); the mixture was stirred at room temperature for 4 h. During this time, a color of the solution turned black. Aqueous $NaHSO_3$ (5%, 10 ml) was added to the mixture; this mixture was extracted with hexane (50 ml×3). The organic layer was dried over $MgSO_4$, and then passed through a short alumina-column in order to remove any trace amount of acetic acid or black impurities. The eluent was concentrated in vacuo to give a colorless oil **4c-2**; yield 1.61 g (92%); bp 238—240 °C/760 mmHg (lit,[20)] bp 120—121 °C/2.5 mmHg).

Ethyl 4,5-Diiodo-2-thiophenecarboxylate (4e-2): Mp 77 °C; ^1H NMR ($CDCl_3$) δ=1.33 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.30 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), and 7.48 (1H, s, 3-H). Found: C, 20.58; H, 1.45%. Calcd for $C_7H_6O_2SI_2$: C, 20.61; H, 1.48%.

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