Halogenation Using Quaternary Ammonium Polyhalides. XXIV.[1] Chlorination of Acetanilides with Benzyltrimethylammonium Tetrachloroiodate

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Synopsis. The reactions of acetanilides with a calculated amount of benzyltrimethylammonium tetrachloroiodate in acetic acid at room temperature or at 70 °C gave, selectively, the desired chloro-substituted acetanilides in good yields.

The chloro-substituted acetanilides **2** have usually been prepared by the *N*-acetylation of chloro-substituted anilines. The direct nuclear chlorination of acetanilides **1** has been scarcely reported. As a novel chlorinating agent for **1**, titanium(IV) chloride in the presence of trifluoroperacetic acid has been used in place of molecular chlorine.[2]

Recent work with this series has shown that benzyltrimethylammonium tetrachloroiodate (BTMA ICl_4) is an excellent chlorinating agent for the nuclear chlorination of aromatic ethers[3] and arenes,[4] and for

Table 1. Chlorination of Acetanilides **1** with BTMA ICl_4 in AcOH

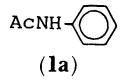
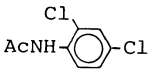
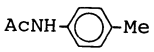
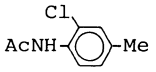
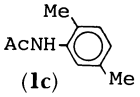
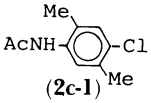
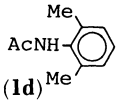
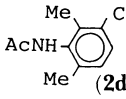
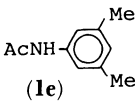
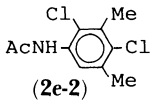
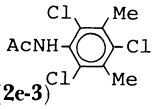
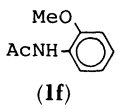
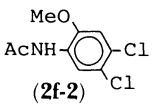
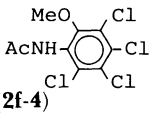
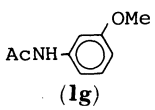
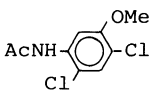
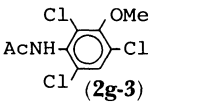
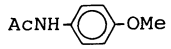
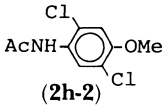
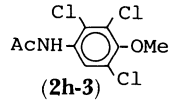
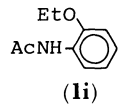
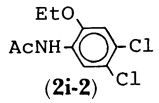
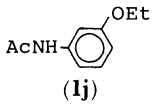
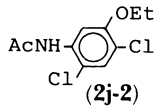
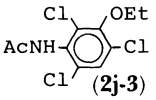
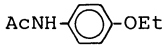
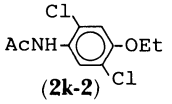
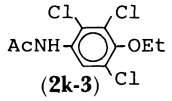
Substrate **1**	Molar ratio BTMA ICl_4/**1**	Reaction conditions Time/h	Temp/°C	Product **2**	Yield[a] %	Mp (°C) found	Mp (°C) reported
 (**1a**)	1.0	24	rt	Mixture[b]	—[b]	—	
1a	4.0	24	70	 (**2a-2**)	87	141—142	143—144[6]
 (**1b**)	1.0	24	rt	 (**2b-1**)	85	113—115	114—115[7]
 (**1c**)	1.0	24	rt	 (**2c-1**)	92	182	177[8]
 (**1d**)	1.0	20	70	 (**2d-1**)	87	148	149—150[9]
 (**1e**)	2.0	24	70	 (**2e-2**)	93	146—147	—
1e	3.0	24	70	 (**2e-3**)	81	223	—
 (**1f**)	2.0	24	rt	 (**2f-2**)	86	134—135	—
1f	4.0	24	70	 (**2f-4**)	85	223—225	—
 (**1g**)	2.0	24	rt	 (**2g-2**)	87	158—159	—

Table 1. (Continued)

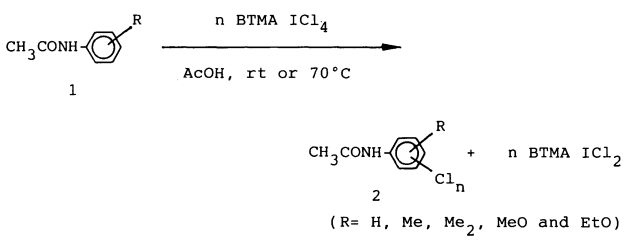
Substrate 1	Molar ratio BTMA ICl_4/1	Reaction conditions Time/h	Temp/°C	Product 2	Yield[a] %	Mp (°C) found	reported
1g	4.0	24	70	 (**2g-3**)	86	184	—
 (**1h**)	2.0	24	rt	 (**2h-2**)	86	189—190	—
1h	3.0	24	70	 (**2h-3**)	91	169—170	—
 (**1i**)	2.0	24	rt	 (**2i-2**)	92	121	—
 (**1j**)	2.0	24	rt	 (**2j-2**)	93	147	—
1j	2.0	24	rt	 (**2j-3**)	82	134—136	—
 (**1k**)	2.0	24	rt	 (**2k-2**)	93	164	164[10]
1k	3.0	24	70	 (**2k-3**)	91	130—131	—

a) Yield of isolated product. b) Product was obtained as a mixture of **2a-1** and **1a**, and the product ratio was determined by its ^1H NMR spectrum as **2a-1**/**1a**=1/2.

the benzylic chlorination of alkyl-substituted aromatic compounds.[5] In this paper we wish to report on the chlorination of **1** by the use of BTMA ICl_4.

Results and Discussion

A reaction of **1** with a calculated amount of BTMA ICl_4 in acetic acid at room temperature or at 70 °C gave **2** together with benzyltrimethylammonium dichloroiodate (BTMA ICl_2). The produced BTMA ICl_2 is so hardly soluble in acetic acid at room temperature that it is easily separable from the reaction mixture. The results are summarized in Table 1, and ^1H NMR and analytical data of the new compounds are shown in Table 2.



Usually, monochloro-substituted acetanilides can be obtained from **1** by the use of an equimolar amount of BTMA ICl_4. Di or trichloro-substituted acetanilides have been obtained by the use of corresponding amounts of BTMA ICl_4. Then, we can selectively prepare the desired chloro-substituted acetanilides by using calculated amounts of BTMA ICl_4.

Exceptionally, as shown in Table 1, the reaction of acetanilide (**1a**) with an equimolar amount of BTMA ICl_4 gave a mixture of 4-chloroacetanilide (**2a—1**) and starting material **1a**. The reaction of 2-methoxyacetanilide (**1f**), 3-methoxyacetanilide (**1g**), and 4-methoxyacetanilide (**1h**) with **1** equiv of BTMA ICl_4 gave a mixture of monochloro-substituted methoxyacetanilides which were governed independently by the orientation of methoxy and acetamido group, respectively. That is, it was difficult to ascertain which orientation was stronger, the methoxy or acetamido group. Pure 2,4-dichloroacetanilide (**2a-2**) and 2,4,6-trichloro-3-methoxyacetanilide (**2g-3**) were obtained from **1a** and 3-methoxyacetanilide (**1g**) with 4 equiv of BTMA ICl_4, respectively.

We believe that the procedure for the chlorination of **1** using BTMA ICl_4 is an efficient method owing to its

Table 2. ^{1}H NMR Data and Analytical Data of **2**

Product	^{1}H NMR ($CDCl_3$/TMS) δ, J/Hz			Found (%) and (Calcd (%))		
	CH_3CONH,	Alkyl or Alkoxy	Aromatic protons	C	H	N
2e-2	2.28 (s, CH_3)	2.44 (s, 5-CH_3) 2.52 (s, 3-CH_3)	8.20 (s, 6-H)	51.89 (51.75	4.78 4.78	6.15 6.03)
2e-3	2.24 (s, CH_3)	2.52 (s, 3 and 5-CH_3)		44.88 (45.06	4.04 3.78	5.23 5.25)
2f-2	2.24 (s, CH_3)	3.96 (s, OCH_3)	7.08 (s, 3-H) 8.48 (s, 6-H)	46.59 (46.18)	3.79 3.87	6.09 5.98)
2f-4	2.16 (s, CH_3) 9.66 (br. s, NH)	3.82 (s, OCH_3)		36.05 (35.68	2.34 2.23	4.48 4.62)
2g-2	2.28 (s, CH_3)	3.96 (s, OCH_3)	7.40 (s, 6-H) 8.28 (s, 3-H)	46.03 (46.18	3.82 3.87	6.03 5.98)
2g-3	2.20 (s, CH_3) 9.04 (br. s. NH)	3.92 (s, OCH_3)	7.44 (s, 5-H)	40.21 (40.26	2.98 3.00	4.95 5.22)
2h-2	2.20 (s, CH_3)	3.92 (s, OCH_3)	7.08 (s, 3-H) 7.92 (s, 6-H)	46.38 (46.18	3.88 3.87	6.01 5.98)
2h-3	2.24 (s, CH_3) 8.80 (br. s, NH)	3.92 (s, OCH_3)	8.12 (s, 6-H)	40.17 (40.26	2.94 3.00	5.03 5.22)
2i-2	2.20 (s, CH_3) 7.72 (br. s, NH)	1.46 (t, J=8 hz, $OCH_2\underline{CH_3}$) 4.04 (q, J=8 hz, $OC\underline{H_2}CH_3$)	6.84 (s, 3-H) 8.48 (s, 6-H)	48.99 (48.41	4.53 4.47	5.54 5.65)
2j-2	2.24 (s, CH_3) 7.60 (br. s, NH)	1.46 (t, J=8 Hz, $OCH_2\underline{CH_3}$) 4.12 (q, J=8 Hz, $OC\underline{H_2}CH_3$)	7.32 (s, 6-H) 8.16 (s, 3-H)	48.30 (48.41	4.42 4.47	5.71 5.65)
2j-3	2.24 (s, CH_3)	1.48 (t, J=8 Hz, $OCH_2\underline{CH_3}$) 4.12 (q, J=8 Hz, $OC\underline{H_2}CH_3$)	7.44 (s, 5-H)	42.55 (42.51	3.69 3.57	4.88 4.96)
2k-3	2.28 (s, CH_3) 7.70 (br. s, NH)	1.48 (t, J=8 Hz, $OCH_2\underline{CH_3}$) 4.12 (q, J=8 Hz, $OC\underline{H_2}CH_3$)	8.40 (s, 6-H)	42.48 (42.51	3.56 3.57	4.82 4.96)

ease, mildness of conditions, and good product yields.

This method afforded good results for the chlorination of **1**, bearing an electron-donating group in their aromatic ring. Unfortunately, the less-reactive **1**, such as nitroacetanilides, gave no products.

Experimental

4-Chloro-2,5-dimethylacetanilide (2c-1); Typical Procedure: BTMA ICl_4 (1.30 g, 3.1 mmol) was added to a solution of 2,5-dimethylacetanilide (**1c**) (0.50 g, 3.10 mmol) in acetic acid (30 ml), and the mixture was stirred for 24 h at room temperature. During this time, BTMA ICl_4 gradually reacted with **1c** to give both a product and a yellow precipitate. The precipitate, which was BTMA ICl_2 (1.06 g, 3.04 mmol), was filtered off. The filtrate was concentrated in vacuo and the residue was treated with 5% $NaHSO_3$ (10 ml) and with 5% $NaHCO_3$ (15 ml), and then extracted with dichloromethane (20 ml×3). The organic layer was separated and a trace amount of acetic acid in the solution was taken away be column chromatography on alumina. The eluent was concentrated in vacuo to give colorless crystals **2c-1**; yield 0.56 g (92%); mp 182 °C (from methanol–water (1:3)) (lit,[8] mp 177 °C).

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