Halogenation Using Quaternary Ammonium Polyhalides. XVII.[1] Iodination of Acetanilide Derivatives with Benzyltrimethylammonium Dichloroiodate and Zinc Chloride

Shoji KAJIGAESHI,* Takaaki KAKINAMI,† Fumiko WATANABE,† and Tsuyoshi OKAMOTO†
Department of Industrial Chemistry, Faculty of Engineering, Yamaguchi University, Tokiwadai, Ube 755
†Department of Industrial Chemistry, Ube Technical College, Tokiwadai, Ube 755
(Received October 24, 1988)

Synopsis. The reaction of acetanilide derivatives with benzyltrimethylammonium dichloroiodate in acetic acid in the presence of $ZnCl_2$ at room temperature or at 70 °C gave iodo-substituted acetanilide derivatives in good yields.

The nuclear iodo-substituted acetanilide derivatives (**2**) have usually been prepared by the *N*-acetylation of iodo-substituted anilines. As an iodinating agent for acetanilide derivatives (**1**) iodine monochloride (ICl) has considerably been used in place of molecular iodine.[2] However, experimental data concerning the direct iodination of **1** have not been appreciably revealed in the literature.

Recent work in this series has shown that benzyltrimethylammonium dichloroiodate (BTMA ICl_2) is an excellent iodinating agent to phenols,[3] aromatic amines,[4] aromatic ethers,[5] and arenes.[6] In this paper we wish to report on the iodination of **1** by the use of BTMA ICl_2 in the presence of $ZnCl_2$.

Results and Discussion

The reaction of **1** with a calculated amount of BTMA ICl_2 and $ZnCl_2$ in acetic acid at room temperature or at 70 °C gave **2** in good yields. The results are summarized in Table 1, and ^1H NMR data and analyt-

Table 1. Iodination of Acetanilide Derivatives by Use of BTMA $ICl_2/ZnCl_2$ in Acetic Acid

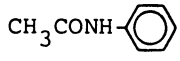
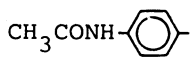
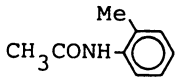
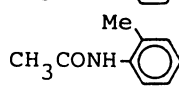
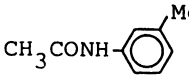
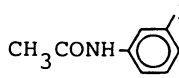
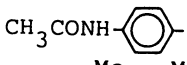
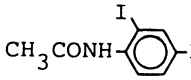
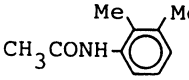
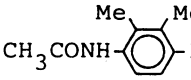
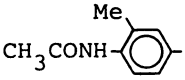
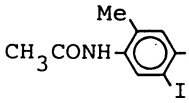
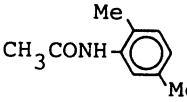
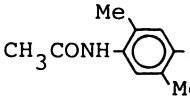
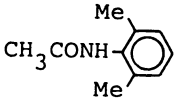
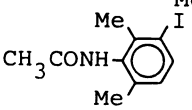
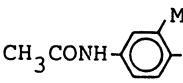
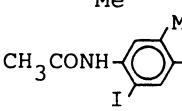
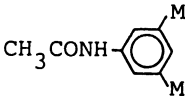
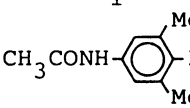
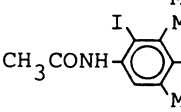
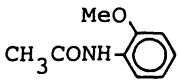
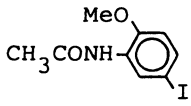
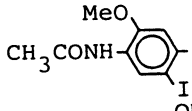
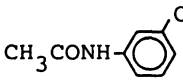
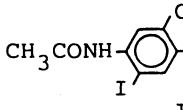
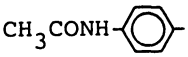
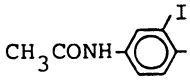
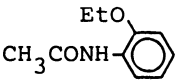
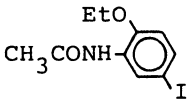
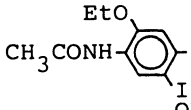
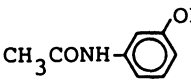
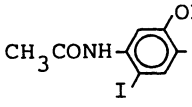
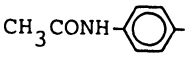
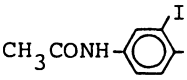
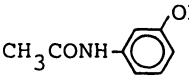
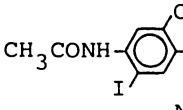
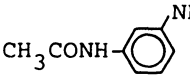
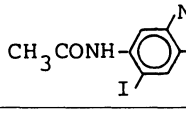
Substrate **1**	Molar ratio BTMA ICl_2/**1**	Reaction conditions Time/h	Temp/°C	Product **2**	Yield[a] %	Mp/°C Found[b]	Mp/°C Reported
 (**1a**)	1.1	2	rt	 (**2a**)	77	186—187	184[2]
 (**1b**)	1.1	4	rt	 (**2b**)	86	172—173	170.5[7]
 (**1c**)	1.1	0.5	rt	 (**2c**)	97	145—146	147—148[8]
 (**1d**)	1.1	24	70	 (**2d**)	76	124—126	133[9]
 (**1e**)	1.1	2	rt	 (**2e**)	88	166—167	—
 (**1f**)	1.1	18	rt	 (**2f**)	73	168—169	—
 (**1g**)	1.1	1	rt	 (**2g**)	91	212—214	—
 (**1h**)	1.1	24	70	 (**2h**)	93	190—192	—
 (**1i**)	1.1	5	rt	 (**2i**)	60	166—167.5	—
 (**1j**)	1.0	1	rt	 (**2j-1**)	80	171—172	—
1j	2.1	16	70	 (**2j-2**)	89	194—195.5	—

Table 1. (Continued)

Substrate 1	Molar ratio BTMA ICl_2/1	Reaction conditions Time/h	Temp/°C	Product 2	Yield[a] %	Mp/°C Found[b]	Mp/°C Reported
 (**1k**)	1.0	2	rt	 (**2k-1**)	67	147—148	—
1k	2.1	21	70	 (**2k-2**)	95	136—137.5	—
 (**1l**)	2.1	1	rt	 (**2l**)	86	210—211	—
 (**1m**)	1.1	48	rt	 (**2m**)	90	149—151	—
 (**1n**)	1.0	3	rt	 (**2n-1**)	82	156—158	—
1n	2.1	21	70	 (**2n-2**)	88	176—177	—
 (**1o**)	2.1	1	rt	 (**2o**)	95	210—211.5	—
 (**1p**)	1.1	48	rt	 (**2p**)	95	140—141	—
 (**1q**)	2.1	3	rt	 (**2q**)	96	223.5—225	—
 (**1r**)	2.1	2	rt	 (**2r**)	84	186—187	172—174[10]

a) Yield of isolated product. b) All new compounds prepared were recrystallized from ethanol-water (1 : 3).

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

Product	^1H NMR ($CDCl_3$/TMS) δ, J/Hz			Found(%) and (Calcd(%))		
	CH_3CONH,	Alkyl or Alkoxyl	Aromatic protons	C	H	N
2e	2.02 (s)	2.15 (s, 2-CH_3)	6.87 (d, J=4, 6-H)	41.42	3.92	4.67
	9.28 (br.s)	2.38 (s, 3-CH_3)	7.53 (d, J=4, 5-H)	(41.54	4.18	4.84)
2f	2.05 (s)	2.12 (s, 2-CH_3)	7.00 (s, 6-H)	41.52	3.92	4.62
	9.03 (br.s)	2.30 (s, 4-CH_3)	7.77 (s, 3-H)	(41.54	4.18	4.84)
2g	2.07 (s)	2.15 (s, 2-CH_3)	7.40 (s, 6-H)	41.52	3.95	4.59
	9.15 (br.s)	2.32 (s, 5-CH_3)	7.60 (s, 3-H)	(41.54	4.18	4.84)
2h	2.07 (s)	2.13 (s, 6-CH_3)	6.77 (d, J=4, 5-H)	41.33	4.11	4.81
	9.23 (br.s)	2.30 (s, 2-CH_3)	7.45 (d, J=4, 4-H)	(41.54	4.18	4.84)
2i	2.07 (s)	2.18 (s, 3 and 4-CH_3)	7.17 (s, 2-H)	41.37	4.39	4.62
	8.93 (br.s)		7.48 (s, 5-H)	(41.54	4.18	4.84)
2j-1	2.08 (s)	2.42 (s, 3 and 5-CH_3)	7.38 (s, 2 and 6-H)	41.51	4.10	4.80
	9.57 (br.s)			(41.54	4.18	4.84)
2j-2	2.07 (s)	2.40 (s, 5-CH_3)	7.20 (s, 6-H)	28.97	2.57	3.35
	9.23 (br.s)	2.87 (s, 3-CH_3)		(28.94	2.67	3.38)
2k-1	2.13 (s)	3.83 (s, OCH_3)	6.73 (d, J=4, 3-H)	37.02	3.34	4.79
	8.90 (br.s)		7.27 (dd, J=4 and 2, 4-H)	(37.14	3.46	4.81)
			8.33 (d, J=2, 6-H)			
2k-2	2.12 (s)	3.82 (s, OCH_3)	7.28 (s, 6-H)	26.09	2.18	3.54
	8.70 (br.s)		8.57 (s, 3-H)	(25.92	2.18	3.36)

Table 2. (Continued)

Product	^{1}H NMR ($CDCl_3$/TMS) δ, J/Hz			Found(%) and (Calcd(%))		
	CH_3CONH,	Alkyl or Alkoxyl	Aromatic protons	C	H	N
21	2.12 (s)	3.80 (s, OCH_3)	7.24 (s, 2-H)	25.83	2.00	3.28
	8.93 (br.s)		8.03 (s, 5-H)	(25.92	2.18	3.36)
2m	2.03(s)	3.77 (s, OCH_3)	6.78 (d, J=4, 5-H)	36.95	3.28	4.78
	9.67 (br.s)		7.47 (dd, J=4 and 2, 6-H)	(27.14	3.46	4.81)
			8.02 (d, J=2, 2-H)			
2n-1	2.12 (s)	1.40 (t, J=7, $OCH_2\underline{CH_3}$)	6.70 (d, J=4, 3-H)	39.23	3.86	4.57
	8.72 (br.s)	4.07 (q, J=7, $OC\underline{H_2}CH_3$)	7.25 (dd, J=4 and 2, 4-H)	(39.36	3.97	4.59)
			8.33 (d, J=2, 6-H)			
2n-2	2.08 (s)	1.37 (t, J=7, $OCH_2\underline{CH_3}$)	7.31 (s, 6-H)	27.90	2.50	3.15
	8.82 (br.s)	4.03 (q, J=7, $OC\underline{H_2}CH_3$)	8.44 (s, 3—H)	(27.87	2.57	3.25)
2o	2.05 (s)	1.35 (t, J=4, $OCH_2\underline{CH_3}$)	7.10 (s, 2-H)	27.82	2.31	3.23
	9.22 (br.s)	4.02 (q, J=4, $OC\underline{H_2}CH_3$)	8.03 (s, 5-H)	(27.87	2.57	3.25)
2p	2.03 (s)	1.37 (t, J=7, $OCH_2\underline{CH_3}$)	6.75 (d, J=4, 5-H)	39.38	3.84	4.55
	9.67 (br.s)	4.00 (q, J=7, $OC\underline{H_2}CH_3$)	7.45 (dd, J=4 and 2, 6-H)	(39.36	3.97	4.59
			8.00 (d, J=2, 2-H)			
2q	2.07 (s)	3.33 (br.s, OH)	7.13 (s, 2-H)	23.84	1.53	3.40
	8.97 (br.s)		7.92 (s, 5-H)	(23.85	1.75	3.48)

ical data of the new **2** are shown in Table 2.

Although BTMA ICl_2 is slightly soluble in acetic acid at room temperature, the addition of $ZnCl_2$ makes this reagent soluble in acetic acid, and the iodination reaction of **1** smoothly proceeds under mild conditions. In this case an equimolar amount of $ZnCl_2$ is required for BTMA ICl_2. Therefore, we assumed the existence of a complex, formed from BTMA ICl_2 with equimolar $ZnCl_2$, as the active species.[6]

We believe that the procedure for the iodination of **1** using BTMA $ICl_2/ZnCl_2$ is an efficient method owing to its ease, mildness of conditions, and good product yields.

As a limitation of this iodinating method, the less reactive **1** such as nitro-, chloro-, and bromoacetanilides gave no product. The reactions of 3-methoxy- (**1l**), 3-ethoxy-(**1o**), 3-hydroxy- (**1q**), and 3-aminoacetanilide (**1r**) with 1-equiv of BTMA $ICl_2/ZnCl_2$ were so vigorous that mixtures of mono, and diiodinated products were obtained, respectively.

Experimental

4-Iodoacetanilide (2a); Typical Procedure: To a solution of acetanilide (**1a**) (0.50 g, 3.70 mmol) in acetic acid (20 ml) was added BTMA ICl_2 (1.42 g, 4.08 mmol) and $ZnCl_2$ (0.7 g, 5.14 mmol). The mixture was stirred for 2 h at room temperature. The yellow color of the solution gradually changed to light brown. The solvent was distilled and a 5% aq solution of $NaHSO_3$ (10 ml) was added to the obtained residue. A 5% aq solution of $NaHCO_3$ was added to the mixture to neutralize; then, the solution was extracted with dichloromethane (40 ml×4). The dichloromethane layer was dried over $MgSO_4$, and passed through a short alumina column. The elute (dichloromethane solution) was concentrated in vacuo to give **2a** as colorless crystals; 0.75 g (77%); mp 186—187 °C (lit,[2] mp 184 °C).

References

1) Part XVI. S. Kajigaeshi, T. Kakinami, M. Shimizu, M. Takahashi, S. Fujisaki, and T. Okamoto, *Tech. Rep. Yamaguchi Univ.*, **4**, 139 (1988).

2) F. D. Chattaway and A. B. Constable, *J. Chem. Soc.*, **105**, 124 (1914).

3) S. Kajigaeshi, T. Kakinami, H. Yamasaki, S. Fujisaki, M. Kondo, and T. Okamoto, *Chem. Lett.*, **1987**, 2109.

4) S. Kajigaeshi, T. Kakinami, H. Yamasaki, S. Fujisaki, and T. Okamoto, *Bull. Chem. Soc. Jpn.*, **61**, 600 (1988).

5) S. Kajigaeshi, T. Kakinami, M. Moriwaki, M. Watanabe, S. Fujisaki, and T. Okamoto, *Chem. Lett.*, **1988**, 795.

6) S. Kajigaeshi, T. Kakinami, M. Moriwaki, T. Tanaka, S. Fujisaki, and T. Okamoto, *Bull. Chem. Soc. Jpn.*, **62**, 439 (1989).

7) H. L. Wheeler and L. M. Liddle, *J. Am. Chem. Soc.*, **42**, 498 (1909).

8) H. Burton and J. Kenner, *J. Chem. Soc.*, **121**, 675 (1922).

9) H. L. Wheeler and L. M. Liddle, *Am. Chem. J.*, **42**, 441 (1909).

10) B. H. Nicolet and J. R. Sampey, *J. Am. Chem. Soc.*, **49**, 1796 (1927).