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

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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

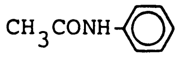
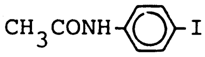
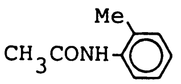
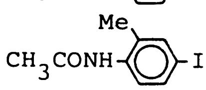
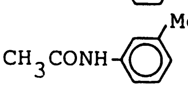
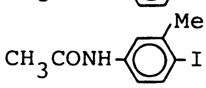
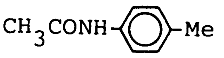
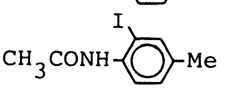
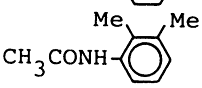
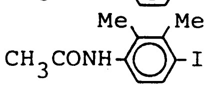
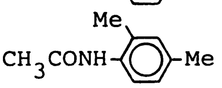
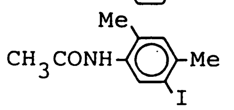
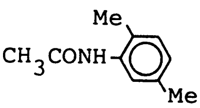
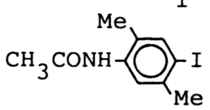
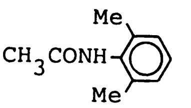
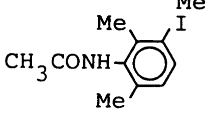
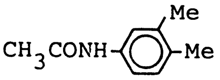
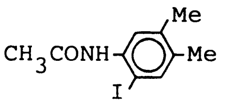
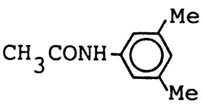
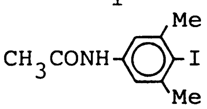
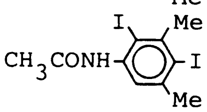
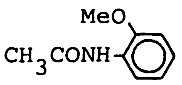
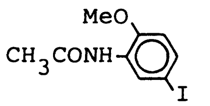
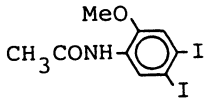
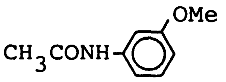
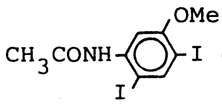
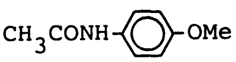
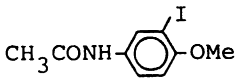
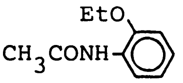
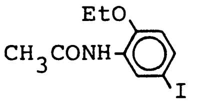
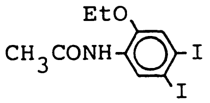
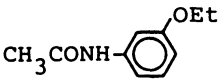
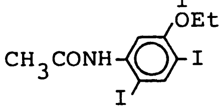
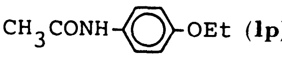
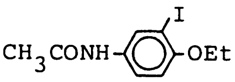
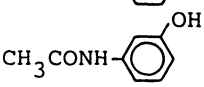
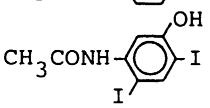
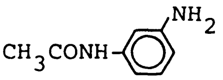
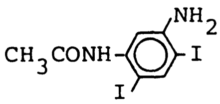
Substrate **1**	Molar ratio BTMA ICl_2/**1**	Reaction conditions Time/h	Temp/°C	Product **2**	Yield[a] %	Mp/°C Found[b]	Reported
 (**1a**)	1.1	2	rt	 (**2a**)	77	186—187	184[2]
 (**1b**)	1.1	4	rt	 (**2b**)	86	172—173	170.5[7]
 (**1c**)	1.1	0.5	rt	 (**2c**)	97	145—146	147—148[8]
 (**1d**)	1.1	24	70	 (**2d**)	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)]	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. ^{1}H NMR Data and Analytical Data of **2**

Product	^{1}H NMR ($CDCl_3$/TMS) δ, J/Hz CH_3CONH,	Alkyl or Alkoxyl	Aromatic protons	Found(%) and (Calcd(%)) 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
2l	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, $OCH_2C\underline{H}_3$)	6.70 (d, J=4, 3-H)	39.23	3.86	4.57
	8.72 (br.s)	4.07 (q, J=7, $OC\underline{H}_2CH_3$)	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, $OCH_2C\underline{H}_3$)	7.31 (s, 6-H)	27.90	2.50	3.15
	8.82 (br.s)	4.03 (q, J=7, $OC\underline{H}_2CH_3$)	8.44 (s, 3—H)	(27.87	2.57	3.25)
2o	2.05 (s)	1.35 (t, J=4, $OCH_2C\underline{H}_3$)	7.10 (s, 2-H)	27.82	2.31	3.23
	9.22 (br.s)	4.02 (q, J=4, $OC\underline{H}_2CH_3$)	8.03 (s, 5-H)	(27.87	2.57	3.25)
2p	2.03 (s)	1.37 (t, J=7, $OCH_2C\underline{H}_3$)	6.75 (d, J=4, 5-H)	39.38	3.84	4.55
	9.67 (br.s)	4.00 (q, J=7, $OC\underline{H}_2CH_3$)	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).

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