

Halogenation Using Quaternary Ammonium Polyhalides. XI.¹⁾ Bromination of Acetanilides by Use of Tetraalkylammonium Polyhalides

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(Received January 11, 1988)

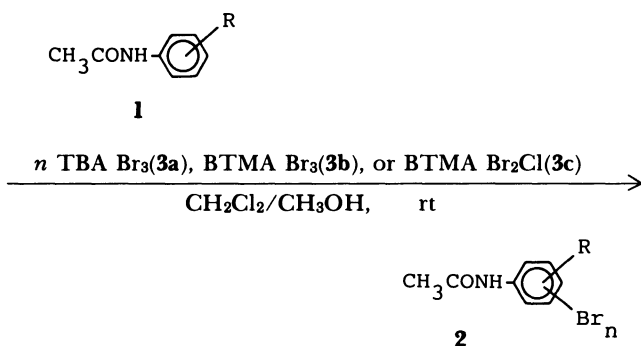
Synopsis. The reaction of acetanilides with tetraalkylammonium polyhalides, such as tetrabutylammonium tribromide, benzyltrimethylammonium tribromide, and benzyltrimethylammonium chlorobromate(1–), in dichloromethane-methanol at room temperature gave bromo-substituted acetanilides in good yields, respectively.

In general, bromo-substituted acetanilides (**2**) have been prepared from the acetylation of bromoanilines with acetyl chloride,²⁾ or acetic anhydride in acetic acid,³⁾ further, from the reaction of acetanilides (**1**) with bromine in acetic acid.⁴⁾ As a special brominating agent for **1**, *N,N*-dibromobenzenesulfonamide has also been used instead of bromine.⁵⁾

Recently, we have shown that benzyltrimethylammonium tribromide (BTMA Br₃) (**3b**) is a useful brominating agent to anilines.⁶⁾ In the present paper, we wish to report on the bromination of **1**, *N*-acetyl-protected anilines, by the use of tetraalkylammonium polyhalides, such as tetrabutylammonium tribromide (TBA Br₃) (**3a**), **3b** and benzyltrimethylammonium chlorobromate(1–) (BTMA Br₂Cl) (**3c**).

Results and Discussion

The reaction of **1** with **3a**,⁷⁾ **3b**,⁸⁾ and **3c** in dichloromethane-methanol at room temperature gave **2** in good yields, respectively.



The results are summarized in Table 1. This table shows that **3c** is the strongest brominating agent to **1**, and that these brominations of **1**, except hydroxy- and amino-substituted acetanilides (e.g., **1h**, **1i**, and **1j**), have usually given predominantly the corresponding para-bromo derivatives.¹⁵⁾ The reaction of hydroxy- or amino-substituted acetanilides with these brominating agents gave mono-, di-, or tribromo-substituted derivatives which were products controlled mainly by

the effect of the hydroxy or amino group on the orientation.

Recently, Berthelot et al.¹⁶⁾ reported that the bromination of **1a** with **3a** in chloroform at room temperature did not proceed at all. However, as shown in the table, in the presence of methanol, the reaction of **1** with **3** in dichloromethane at room temperature easily gave **2** in good yields. In these cases, it can be presumed that the active species is probably the methyl hypobromite produced from the reaction of **3** with methanol.¹⁷⁾

Since aminophenols and phenylenediamines are so sensitive for **3**, isolations of mono-, di-, or tribromo derivatives of these compounds are considerably difficult. However, the selective brominations of *N*-acetyl-protected anilines, such as 2-hydroxyacetanilide (**1h**), 3-hydroxyacetanilide (**1i**), and 3-aminoacetanilide (**1j**), by use of **3** under mild conditions occurred most readily, as shown in the table. Accordingly, bromo-substituted aminophenols and phenylenediamines should be obtained by the hydrolyses of these corresponding acetanilides.

We believe that these tetraalkylammonium polyhalides such as TBA Br₃, BTMA Br₃, and BTMA Br₂Cl are more useful brominating agents for **1** than bromine or *N,N*-dibromobenzenesulfonamide, because of their solid character, stability and nontoxicity.

Experimental

Benzyltrimethylammonium Chlorobromate(1–) (BTMA Br₂Cl) (3c**).** To a solution of bromine (15.98 g, 0.1 mol) in dichloromethane (100 ml) was added dropwise a solution of benzyltrimethylammonium chloride (18.57 g, 0.1 mol) in water (100 ml) under stirring at room temperature. After the mixture was stirred for 30 min, the dichloromethane layer was separated and dried with magnesium sulfate, and then evaporated in vacuo to give a residue which was recrystallized from dichloromethane-ether (10:1) affording BTMA Br₂Cl as stable orange crystals; yield 24.50 g (71%); mp 101–102 °C. Found: C, 34.88; H, 4.63; N, 4.01; Br₂Cl, 56.31%. Calcd for C₁₀H₁₆NBr₂Cl: C, 34.76; H, 4.67; N, 4.05; Br₂Cl, 56.51%.

4-Bromoacetanilide (2a**); Typical Procedure:** To a solution of acetanilide (**1a**) (0.50 g, 3.70 mmol) in dichloromethane (50 ml)-methanol (20 ml) was added **3c** (1.41 g, 4.08 mmol) at room temperature. The mixture was stirred for 20 min until a decoloration of the orange color took place. The solvent was distilled and to the obtained residue was added water (20 ml). The mixture was extracted with ether (40 ml×4). The ether layer was then dried with

Table 1. Bromination of Acetanilides by Use of Tetraalkylammonium Polyhalides

	Substrate 1	Product 2	Molar ratio 3/1	3 used	Reaction time	Yield ^{a)} /%	Mp θ_m /°C	
							Found	Reported
a			1.1	3a	12 h	95	163—164	168.8 ⁹⁾
				3b	2 h	97		
				3c	20 min	97		
b			1.1	3a	36 h	91	160	158—159 ¹⁰⁾
				3b	27 h	87		
				3c	10 h	99		
c			1.1	3a	1 h	98	103—104	103—104 ¹¹⁾
				3b	3 h	96		
				3c	15 min	99		
d			1.1	3a	12 h	95	159—160	161—162 ³⁾
				3b	2 h	96		
				3c	2 h	89		
e			1.1	3a	12 h	96	188	187 ⁴⁾
				3b	2 h	95		
				3c	20 min	93		
f			1.1	3a	12 h	91	163—164	164 ¹²⁾
				3b	16 h	92		
				3c	15 min	91		
g			1.1	3a	10 min	97	180—181	—
				3b	2 min	96		
				3c	1 min	96		
h-1			1.0	3a	15 min	97	175—176	175—175.5 ¹³⁾
				3b	2 min	99		
				3c	1 min	96		
h-2			2.1	3a		— ^{b)}	174	174—175 ¹⁴⁾
				3b		— ^{b)}		
				3c	2 h	89		
i-1			2.0	3a	1 h	93	237—238	—
				3b	1 h	92		
				3c	2 min	88		
i-2			3.1	3a		— ^{c)}	205	—
				3b	24 h	69		
				3c	14 h	93		
j-1			2.0	3a	10 min	96	162—163	—
				3b	3 min	91		
				3c	— ^{d)}	96		
j-2			3.1	3a		— ^{c)}	218—218.5	—
				3b	21 h	57		
				3c	3 h	98		

a) Yield of isolated product. b) A mixture of mono- and dibromo compounds was obtained. c) A mixture of di- and tribromo compounds was obtained. d) Product 2j-1 precipitated almost immediately as soon as the solution of 3c was added into the solution of 1j.

magnesium sulfate and evaporated in vacuo to give a residue which was recrystallized from ethanol-water (1:3) affording 2a as colorless crystals; yield 0.77 g (97%); mp 163—164 °C (lit.⁹⁾ mp 168.8 °C).

4-Bromo-3,5-dimethylacetanilide (2g). Compound 2g was prepared from the reaction of 3,5-dimethylacetanilide (1g) with equimolecular amount of 3 by a similar procedure to that described above: colorless crystals; mp 180—181 °C

(ethanol-water (1:3)): IR (KBr) 1670 cm⁻¹ (CO); ¹H NMR (CDCl₃) δ =2.05 (3H, s, COCH₃), 2.34 (6H, s, 3 and 5-CH₃), 7.34 (2H, s, 2 and 6-H), 9.63 (1H, br. s, NH). Found: C, 49.58; H, 4.92; N, 5.74%. Calcd for C₁₀H₁₂NOBr: C, 49.61; H, 4.99; N, 5.79%.

2,4-Dibromo-5-hydroxyacetanilide (2i-1). Compound 2i-1 was prepared from 3-hydroxyacetanilide (1i) and 2 equiv of 3 by a similar procedure to that described above: colorless

crystals; mp 237–238 °C (ethanol–water (1:3)); IR (KBr) 1680 cm⁻¹ (CO); ¹H NMR (CDCl₃) δ=2.17 (3H, s, CH₃), 7.55 (1H, s, 6-H), 7.75 (1H, s, 3-H), 8.38 (1H, br. s, OH), 10.08 (1H, br. s, NH). Found: C, 30.98; H, 2.19; N, 4.49%. Calcd for C₈H₇NO₂Br₂: C, 31.10; H, 2.29; N, 4.53%.

3-Hydroxy-2,4,6-tribromoacetanilide (2i-2). Compound **2i-2** was prepared similarly from **1i** and 3 equiv of **3b** or **3c**: colorless crystals, mp 205 °C (ethanol–water (1:3)); IR (KBr) 1675 cm⁻¹ (CO); ¹H NMR (CDCl₃) δ=2.08 (3H, s, CH₃), 3.50 (1H, br. s, OH), 7.73 (1H, s, 5-H), 9.69 (1H, br. s, NH). Found: C, 24.81; H, 1.60; N, 3.60%. Calcd for C₈H₆NO₂Br₃: C, 24.77; H, 1.56; N, 3.61%.

5-Amino-2,4-dibromoacetanilide (2j-1). Compound **2j-1** was prepared similarly from **1j** and 2 equiv of **3**: colorless crystals, mp 162–163 °C (ethanol–water (1:3)); IR (KBr) 1655 cm⁻¹ (CO); ¹H NMR (CDCl₃) δ=2.12 (3H, s, CH₃), 4.25 (2H, br. s, NH₂), 7.38 (1H, s, 6-H), 7.45 (1H, s, 3-H), 8.67 (1H, br. s, NH). Found: C, 30.97; H, 2.52; N, 8.90%. Calcd for C₈H₈N₂OBr₂: C, 31.20; H, 2.62; N, 9.10%.

3-Amino-2,4,6-tribromoacetanilide (2j-2). Compound **2j-2** was prepared similarly from **1j** and 3 equiv of **3b** or **3c**: colorless crystals, mp 218–218.5 °C (ethanol–water (1:3)); IR (KBr) 1675 cm⁻¹ (CO); ¹H NMR (CDCl₃) δ=2.10 (3H, s, CH₃), 4.28 (2H, br. s, NH₂), 7.62 (1H, s, 5-H), 9.48 (1H, br. s, NH). Found: C, 24.97; H, 1.79; N, 6.98%. Calcd for C₈H₇N₂OBr₃: C, 24.84; H, 1.82; N, 7.24%.

We wish to thank Dr. Mamoru Nakai and Mr. Katsumasa Harada, Ube Laboratory, Ube Industries, Ltd., for elemental analysis.

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