Halogenation Using Quaternary Ammonium Polyhalides. IV.[1] Selective Bromination of Phenols by Use of Tetraalkylammonium Tribromides

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Synopsis. Reaction of phenols with calculated amounts of benzyltrimethylammonium tribromide or tetrabutylammonium tribromide in dichloromethane–methanol for 0.5—1 h under mild conditions gave, selectively, the objective mono-, di-, or tribromophenols in good yields.

Previous work in this series[2] has shown that the reaction of phenols (**1**) with benzyltrimethylammonium tribromide (BTMA Br_3) (**2a**) in dichloromethane–methanol at room temperature readily gave bromophenols (**3**). In this paper, we wish to report a selective bromination of **1** by use of tetraalkylammonium tribromides (**2**), such as **2a** or tetrabutylammonium tribromide (TBA Br_3) (**2b**).

Results and Discussion

In general, it is difficult to carry out a step-by-step bromination of **1** with bromine since **1** reacts very rapidly with the reagent and leads to the polybromo-substituted phenols. For the purpose of the syntheses of monobromophenols from **1**, some technique in which the position of the substrate is blocked by an appropriate substituent group has frequently been employed.[3,4]

The well-known method for preparing pure monobromophenols is a diazotization of the corresponding aromatic amines and a subsequent heating with water. However, sometimes this method requires a tediously long synthetic pathway to obtain the bromophenols.

We have recently found that the reaction of **1** with calculated amounts of **2a** or **2b** in dichloromethane–methanol at room temperature gives the desirable mono-, di-, or tribromophenols in good yields. For instance, reactions of phenol (**1a**) with 1.0 equiv of **2b** gave *p*-bromophenol (**3a-1**), and with 2.0 equiv of **2a** gave 2,4-dibromophenol (**3a-2**); furthermore, reactions with 3.0 equiv of **2a** gave 2,4,6-tribromophenol[2] in good yields, respectively. Especially, we emphasize that our procedure is a highly useful method for synthesizing monobromophenols. The results are summarized in the Table 1. (The results for an exhaustive bromination of several **1** with sufficient amounts of **2a** are already shown by us[2]).

Compounds 2,4-dibromophenol[6] (**3a-2**), 2-bromo-4-*t*-butylphenol[12] (**3e-1**) and 2,4,6-tribromo-1,3-benzenediol[24] (**3m-2**) have been prepared by special methods. Our method easily gave these compounds in good yields, respectively. However, as a limitation of this method, attempts at the monobromination of less reactive **1**, such as nitrophenols, were unsuccessful.[28]

Experimental

4-Bromo-3,5-dimethylphenol (3i-1): Typical Procedure (1). To a solution of 3,5-dimethylphenol (**1i**) (0.50 g, 4.09 mmol) in dichloromethane (30 ml)–methanol (20 ml) was added dropwise **2b** (2.0 g, 4.13 mmol) under stirring at room temperature. The mixture was stirred for 30 min until a decoloration of the orange solution took place. The solvent was distilled and to the obtained residue was added water (30 ml). The mixture was extracted with ether (40 ml×4). The ether layer was then dried with magnesium sulfate and evaporated in vacuo to give a residue which was recrystallized from methanol–water (1:3) affording **3i-1** as colorless crystals; yield 0.77 g (93%); mp 115—116 °C (lit,[18] mp 115—116 °C).

2,4-Dibromo-3,5-dimethylphenol (3i-2): Typical Procedure (2). To a solution of **1i** (0.50 g, 4.09 mmol) in dichloromethane (30 ml)–methanol (20 ml) was added dropwise **2a** (3.2 g, 8.23 mmol) under stirring at room temperature. The mixture was stirred for 30 min until a decoloration of the orange solution took place. A subsequent same work-up as above gave **3i-2** as colorless crystals; yield 1.07 g (93%); mp 72—73 °C (lit,[18] mp 72—73 °C).

2,4,6-Tribromo-3,5-dimethylphenol (3i-3): Typical Procedure (3). A mixture of **1i** (0.50 g, 4.09 mmol) and **2a** (4.95 g, 12.70 mmol) in dichloromethane (50 ml)–methanol (20 ml) was stirred for 1 h at room temperature until a discoloration of the orange solution took place. A subsequent same work-up as above gave **3i-3** as colorless crystals; yield 1.63 g (90%); mp 166—169 °C (lit,[19] mp 166 °C).

References

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Table 1. Bromophenols(**3**) from Phenols(**1**) Using Tetraalkylammonium Tribromides(**2**)

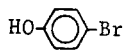
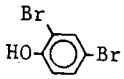
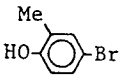
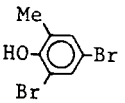
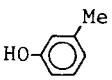
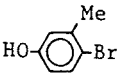
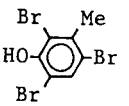
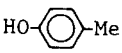
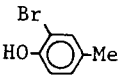
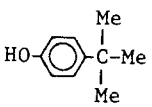
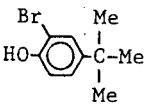
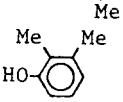
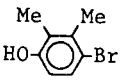
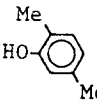
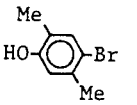
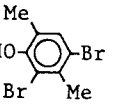
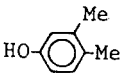
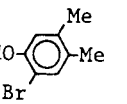
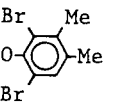
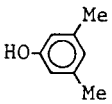
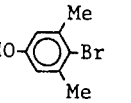
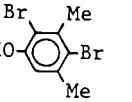
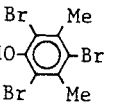
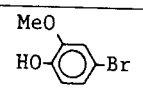
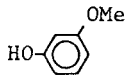
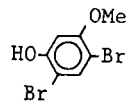
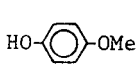
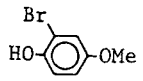
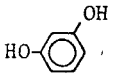
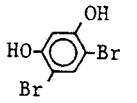
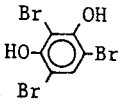
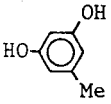
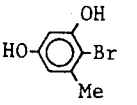
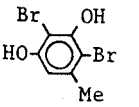
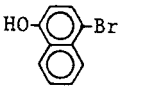
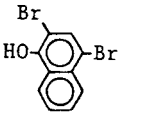
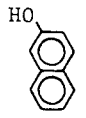
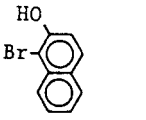
Phenols(**1**)		Product(**3**)		**2** used	Molar ratio (**2**/**1**)	Yield[a] %	Mp(θ_m/°C) or Bp(θ_b/°C) Found	Reported
	(**1a**)		(**3a-1**)	**2b**	1.0	93	61—63	63[5]
			(**3a-2**)	**2a**	2.0	87	38—39	40[6]
	(**1b**)		(**3b-1**)	**2b**	1.0	93	62—63	64[7]
			(**3b-2**)	**2a**	2.1	91	56.5	57[8]
	(**1c**)		(**3c-1**)	**2b**	1.0	93	59—61	62[9]
			(**3c-2**)	**2a**	3.1	93	81	81—82[10]
	(**1d**)		(**3d-1**)	**2b**	1.0	90	218—219/ 760 mmHg	218—219/[11] 760 mmHg
	(**1e**)		(**3e-1**)	**2a**	1.0	89	49—52	52[12]
	(**1f**)		(**3f-1**)	**2b**	1.0	93	89—91	92[13]
	(**1g**)		(**3g-1**)	**2b**	1.0	93	86—87	87[14]
			(**3g-2**)	**2a**	2.1	93	79	79—80[15]
	(**1h**)		(**3h-1**)	**2b**	1.0	93	78—79	80[16]
			(**3h-2**)	**2a**	2.1	93	38—40	39—40[17]
	(**1i**)		(**3i-1**)	**2b**	1.0	93	115—116	115—116[18]
			(**3i-2**)	**2a**	2.0	93	72—72	72—73[18]
			(**3i-3**)	**2a**	3.1	90	166—169	166[19]

Table 1. (Continued)

Phenols(1)		Product(3)		2 used	Molar ratio (2/1)	Yield[a] %	Mp(θ_m/°C) or Bp(θ_b/°C) Found	Reported
	(**1j**)		(**3j-1**)	**2b**	1.0	90	35—39	46[20]
	(**1k**)		(**3k-1**)	**2a**	2.0	93	65—66	73—75[21]
	(**1l**)		(**3l-1**)	**2b**	1.0	90	42—43	45[22]
	(**1m**)		(**3m-1**)	**2a**	2.0	92	109—110	110—112[23]
			(**3m-2**)	**2a**	3.1	93	111.5—113.5	112[24]
	(**1n**)		(**3n-1**)	**2b**	1.0	93	132—135	135[25]
			(**3n-2**)	**2a**	2.0	93	125—126	124—125[26]
	(**1o**)		(**3o-1**)	**2b**	1.0	93	127	127—128[27]
			(**3o-2**)	**2a**	2.0	93	107—108	105.5[27]
	(**1p**)		(**3p-1**)	**2b**	1.0	93	84	84—85[27]

a) Yield of isolated product. 1 mmHg = 133.322 Pa.

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28) For instance, the reaction of 4-nitrophenol with 1.0 equiv of **2a** in dichloromethane–methanol for 1 h at room temperature gave a mixture of 2,6-dibromo-4-nitrophenol and 4-nitrophenol recovered in the ratio of 1:1 on ^{1}H NMR spectra.