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Bromination of Phenols by Use of Benzyltrimethylammonium Tribromide

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The reaction of phenols with benzyltrimethylammonium tribromide in dichloromethane-methanol for 1 h at room temperature gave polybromophenols in good yields.

Organic ammonium tribromides, such as pyridinium tribromide,[1] phenyltrimethylammonium tribromide,[2,3] tetramethylammonium tribromide,[4] and tetrabutylammonium tribromide[5] have been used as mild and selective brominating agents. These reagents have a merit to be treated quantitatively compared with liquid bromine because of their solid character. In the present paper, we wish to report a facile synthetic procedure of bromophenols (1) by the use of a new reagent, benzyltrimethylammonium tribromide (BTMA Br_3).

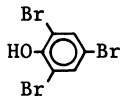
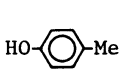
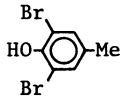
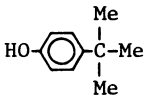
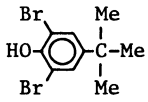
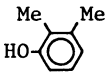
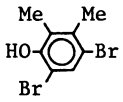
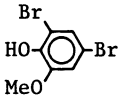
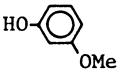
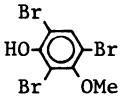
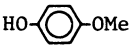
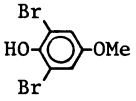
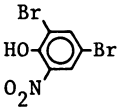
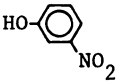
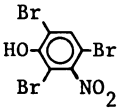
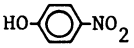
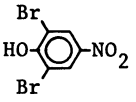
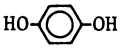
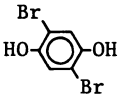
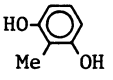
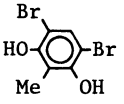
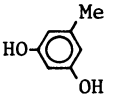
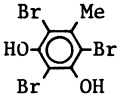
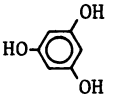
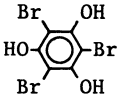
Reaction of benzyltrimethylammonium chloride with bromine in dichloromethane gave BTMA Br_3, which was also prepared by the additiion of hydrobromic acid to an aqueous solution of benzyltrimethylammonium chloride and sodium bromate in good yield.

Reaction of phenols (2) with BTMA Br_3 in a dichloromethane-methanol for 1 h at room temperature gave readily 1 in good yields. The result are summarized in the Table 1.

In the case of the preparation of 2,4,6-tribromophenol (1a), 3-methoxy-2,4,6-tribromophenol (1f), 2,4-dibromo-6-nitrophenol (1h), 3-nitro-2,4,6-tribromophenol (1i), and 2,6-dibromo-4-nitrophenol (1j), calcium carbonate powder (equivalent weight with used BTMA Br_3) was employed in order to neutralize a generating hydrogen bromide.

Preparation of polybromomethoxyphenols by use of bromine is usually

Table 1. Polybromophenols(1) from Phenols(2)

	Substrate(2)	Product(1)	Molar ratio ($BTMABr_3$/2)	Yield[a] %	Mp θm/°C found	Mp θm/°C reported
a [b]			3.1	92	91-92	95[6]
b			2.1	93	50	49[7]
c			2.1	93	70-71	70-71[8]
d		 [9]	2.1	93	67-68	-
e			2.1	90	60-61	64-65[10]
f [b]			3.1	92	104-105	104[11]
g		 [12]	2.1	91	83-84	-
h [b]			2.1	93	111-113	118[13]
i [b]			3.1	90	88-89	89-90[14]
j [b]			2.1	90	144-145.5	144[15]
k			2.1	84	183-185	186[16]
l			2.1	93	101.5-102.5	102[17]
m			3.1	92	98-99	98[18]
n			3.1	93	153-154.5	152-153[19]

a) Yield of isolated product. b) $CaCO_3$ powder was used.

difficult. Particularly, 2,4-dibromo-6-methoxyphenol (1e) have been prepared from guaiacol (2e) in a tedious long synthetic pathway.[10] However, 1e was obtained by our method with only one-step from 2e in 90% yield. Bromination of 4-nitrophenol (2j) have been carried out with unusual reagent bromine chloride.[15] The compounds 1h, 1i, and 1j were easily prepared using calcium carbonate powder as described above. Compounds 2,6-dibromo-4-tert-butylphenol[8] (1c), 4,6-dibromo-3-hydroxy-2-methylphenol[17] (1l), and tribromophloroglucinol[19] (1n) have been prepared by special methods. Our methods easily gave these compounds in good yields, respectively.

Because the presence of methanol markedly facilitates the bromination of 2,[20] it can be presumed that active species which generates Br^+ is probably methyl hypobromite produced from the reaction of BTMA Br_3 with methanol. In fact, we confirmed the evolution of hydrogen bromide by the addition of BTMA Br_3 to methanol at room temperature. The reaction of 2 with the active intermediate methyl hypobromite must give 1 and methanol which can be employed repeatedly.

$$PhCH_2(CH_3)_3N^+Br_3^- + CH_3OH \longrightarrow PhCH_2(CH_3)_3N^+Br^- + CH_3OBr + HBr$$

$$2 + CH_3OBr \longrightarrow 1 + CH_3OH$$

We emphasize that the procedure for bromination of phenols will be a highly useful method because of its ease, simplicity, excellent yield of product, and mildness of conditions.

A general procedure is as follows: To a solution of 4-methylphenol (2b) (0.50 g, 4.62 mmol) in dichloromethane (50 ml)-methanol (20 ml) was added BTMA Br_3 (3.8 g, 9.72 mmol) at room temperature. The mixture was stirred for 1 h until a decoloration of orange solution took place. The solvent was distilled and the solid residue was extracted with ether (40 ml x 4). The ether layer was dried with magnesium sulfate and evaporated in vacuo to give the residue which was recrystallized from methanol-water (1 : 3) affording 2,6-dibromo-4-methylphenol (1b) as colorless needles; yield 1.15 g.

A procedure using $CaCO_3$ is as follows: To a solution of phenol (2a) (0.50 g, 5.31 mmol) in dichloromethane (50 ml)-methanol (20 ml) was added BTMA Br_3 (6.42 g,

16.5 mmol) and calcium carbonate powder (2 g, 20 mmol) at room temperature. After one hour stirring, decoloration of orange solution took place. The solid calcium carbonate was filtered off, the filtrate was concentrated and to the obtained residue was added water (20 ml). The mixture was extracted with ether (40 ml x 4). The ether layer was dried with magnesium sulfate and evaporated in vacuo to give 1a as colorless needles (from methanol-water (1 : 3)); yield 1.61 g.

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9) 4,6-Dibromo-2,3-dimethylphenol (1d): mp 67-68 °C (from methanol-water (1 : 3)); ^{1}H NMR ($CDCl_3$) δ = 2.25 (6H, br.s, $2CH_3$), 5.35 (1H, s, OH), and 7.42 (1H, s, 5-H). Found: C, 34.17; H, 2.90; Br, 56.88%. Calcd for $C_8H_8OBr_2$: C, 34.32; H, 2.88; Br, 57.08%.
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12) 2,6-Dibromo-4-methoxyphenol (1g): mp 83-84 °C (from methanol-water (1 : 3)); ^{1}H NMR ($CDCl_3$) δ = 3.72 (3H, s, OCH_3), 5.45 (1H, br.s, OH), and 6.98 (2H, s, 3- and 5-H). Found: C, 30.03; H, 2.33; Br, 56.53%. Calcd for $C_7H_6O_2Br_2$: C, 29.82; H, 2.51; Br, 56.68%.
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18) R. L. Datta and J. C. Bhoumik, J. Am. Chem. Soc., 43, 309 (1921).
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20) In the case of the absence of methanol, the reaction of 3-methoxyphenol (2f) with BTMA Br_3 and $CaCO_3$ in dichloromethane for 1 h at room temperature gave a mixture of 4,6-dibromo-3-methoxyphenol and 1f in the ratio of 3 : 1 on ^{1}H NMR spectra. The same treatment of 2j gave 1j in 30% yield and 2j was recovered in 70%.

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