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Iodination of Phenols by Use of Benzyltrimethylammonium Dichloroiodate(1−)[1)]

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The reaction of phenols with benzyltrimethylammonium dichloroiodate(1−) in dichloromethane-methanol in the presence of $CaCO_3$ or $NaHCO_3$ for several hours at room temperature gave iodophenols in good yields.

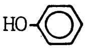
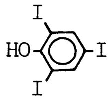
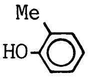
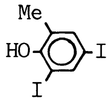
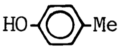
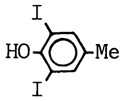
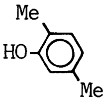
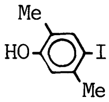
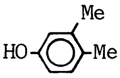
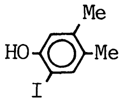
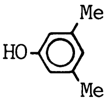
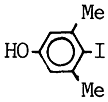
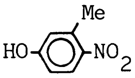
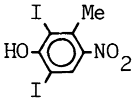
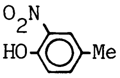
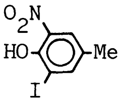
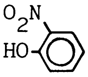
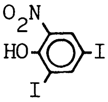
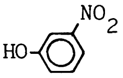
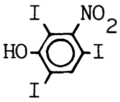
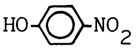
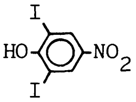
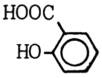
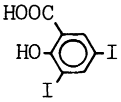
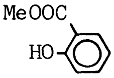
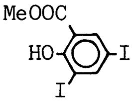
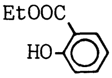
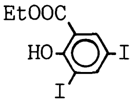
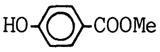
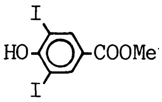
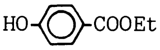
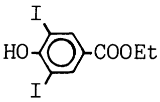
Usually, iodine is the least reactive halogens in aromatic substitution, and reversibility between iodine and produced hydrogen iodide is so important that the reaction is seldom practicable unless some species is present to remove the hydrogen iodide as soon as it is formed. For that purpose, HgO, HNO_3, HIO_3 and H_2O_2 have been used as the species to oxidize the hydrogen iodide. For the iodination of phenols and hydroxybenzoic acids, iodine monochloride (ICl) is a better reagent than iodine itself.[2)]

Now, we found that a new reagent benzyltrimethylammonium dichloroiodate(1−) (BTMA ICl_2), easily prepared from benzyltrimethylammonium chloride and ICl, was a highly useful reagent for the aromatic electrophilic iodination. In this paper, we wish to report a facile synthesis of iodophenols (1) from phenols (2) by use of BTMA ICl_2.

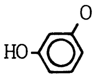
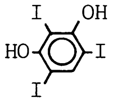
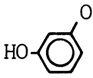
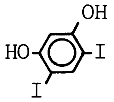
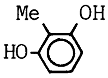
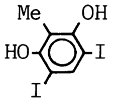
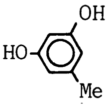
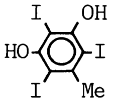
Reaction of 2 with BTMA ICl_2 in dichloromethane-methanol in the presence of powdered $CaCO_3$ or $NaHCO_3$ for several hours at room temperature gave 1 in good yields. The results are summarized in Table 1. In these reactions, $NaHCO_3$ was used for the iodination of phenols bearing electron-attracting groups, because $NaHCO_3$ should activate these inactive aromatic ring by the formation of phenolate ion. On the other hand, $CaCO_3$ was used for the iodination of phenols bearing electron-releasing substitutions, because use of $NaHCO_3$ made their reactions too vigorous accompanying oxidation.

We noticed that the presence of methanol markedly facilitated the iodination of 2.[16)] In this case, the main active species is probably methyl hypoiodite produced from reaction of BTMA ICl_2 with methanol. Reaction of 2 with methyl hypoiodite must give 1 and methanol which can be employed repeatedly. Hydrogen chloride generated should be neutralized by added $CaCO_3$ or $NaHCO_3$. Thus, our method requires no oxidant for the iodination of 2.

Table 1. Iodophenols(1) from Phenols(2) and BTMA ICl_2 in CH_2Cl_2-CH_3OH at Room Temperature

	Substrate(2)	Product(1)[a]	Reaction time/ h	Molar ratio (BTMA ICl_2/2)	Yield[b] %	Mp θm/°C found	Mp θm/°C reported
a [c]			7	3.1	72	159-160	158.5-159[3]
b [d]			4	2.1	70	62-64	67[4]
c [d]			4	2.1	87	60-61	61.5[4]
d [d]			4	1.1	71	95-96	98[5]
e [d]			4	1.1	63	61-63.5	66-67[5]
f [d]			4	1.1	67	125-126	131[6]
g [c]		 [7]	6	2.1	95	113-114	-
h [c]			6	1.1	95	82-83	83.5[4]
i [c]			7	2.1	96	98	98[4]
j [c]			7	3.1	95	140-141	137[8]
k [c]			7	2.1	96	157-158	157[4]
l [c]			7	2.1	91	233	235-236[9]
m [c]			7	2.1	96	109-110	110[10]
n [c]			7	2.1	92	131-132	133[10]
o [c]			7	2.1	75	164-165	166-167[11]
p [c]			7	2.1	92	119-122	123-124[11]

Continued

q d)			4	3.1	95	154-155	154[12)]
r d)e)			12	3.1	94	145-146	145[13)]
s d)		 14)	4	2.1	95	119-121	-
t d)			4	3.1	90	163-165	161-164[15)]

a) Structures of known products were also confirmed by their ^{1}H NMR spectra.

b) Yield of isolated product. *c)* $NaHCO_3$ was used. *d)* $CaCO_3$ was used.

e) This run was done in dichloromethane without methanol.

$$PhCH_2(CH_3)_3N^+ICl_2^- \quad + \quad CH_3OH$$

$$\longrightarrow \quad PhCH_2(CH_3)_3N^+Cl^- \quad + \quad CH_3OI \quad + \quad HCl$$

$$\underline{2} \quad + \quad CH_3OI \quad \longrightarrow \quad \underline{1} \quad + \quad CH_3OH$$

The reagent BTMA ICl_2 (stable yellow crystals, mp 125-126 °C) has a merit in that it can be quantitatively treated compared with viscous ICl, because of its solid character. Furthermore, iodination of 2 using BTMA ICl_2 is carried out in CH_2Cl_2 at room temperature and the solvent can be easily distilled away. Whereas, ICl is usually used in acetic acid under heating conditions.[9)]

Although preparation of iodo-substituted nitrophenols, hydroxybenzoic acids and their esters are usually difficult, our method gave easily these iodination products in good yields. It can be emphasized that BTMA ICl_2 is an excellent and unique iodinating agent for phenols.

Preparation of BTMA ICl_2 is as follows: To a black solution of ICl (16.20 g, 0.1 mol) in dichloromethane (200 ml) was added dropwise a solution of benzyltrimethylammonium chloride (18.60 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, dried with $MgSO_4$, and then evaporated in vacuo to give the residue, which was recrystallized from dichloromethane-ether (3 : 1) to afford BTMA ICl_2 as brilliant yellow needles; yield 30.0 g (86%); mp 125-126 °C. Found: C, 34.51; H, 4.67; N, 4.11%. Calcd for $C_{10}H_{16}NCl_2I$: C, 34.50; H, 4.63; N, 4.03%.

A typical procedure is illustrated for the synthesis of 2,4,6-triiodophenol (1a): To a solution of phenol (2a)(0.50 g, 5.31 mmol) in dichloromethane (50 ml)-methanol (20 ml) were added BTMA ICl_2 (5.73 g, 16.46 mmol) and $NaHCO_3$ (3 g). The mixture was stirred for 7 h at room temperature. A yellow color of the solution gradually changed to light brown. An excess $NaHCO_3$ was filtered off and the filtrate was concentrated and then aqueous $NaHCO_3$ (5%, 20 ml) was added to the residue obtained. The mixture was extracted with ether (40 ml x 4). The ethereal layer was dried with $MgSO_4$ and evaporated in vacuo to give 1a as colorless needles (from 1:3 methanol-water); yield 1.81 g.

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References

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7) 2,6-Diiodo-3-methyl-4-nitrophenol (1g): mp 113-114 °C (from methanol-water (1 : 3)). ^1H NMR ($CDCl_3$) δ= 2.67 (3H, s, CH_3), 6.35 (1H, br.s, OH), and 8.23 (1H, s, 5-H). Found: C, 20.77; H, 1.02; N, 3.17%. Calcd for $C_7H_5NO_3I_2$: C, 20.76; H, 1.24; N, 3.46%.
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14) 4,6-Diiodo-2-methyl-1,3-benzenediol (1s): mp 119-121 °C (from methanol-water (1 : 3)). ^1H NMR ($CDCl_3$) δ= 2.27 (3H, s, CH_3), 6.35 (2H, br.s, OH), and 7.73 (1H, s, 5-H). Found: C, 22.32; H, 1.51%. Calcd for $C_7H_6O_2I_2$: C, 22.36: H, 1.61%.
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16) In the case of the absence of methanol, the reaction of 1,3-benzenediol (2r) with BTMA ICl_2 in dichloromethane for 12 h at room temperature gave 4,6-diiodo-1,3-benzenediol (1r). However, the treatment of 2r with BTMA ICl_2 in dichloromethane-methanol solution for 4 h gave 2,4,6-triiodo-1,3-benzenediol (1q).

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