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Benzalkonium Tribromide, Synthesis and Utilization in Phenols Bromination Processes †

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Abstract: The classic bromination of aromatic substrates is carried out, conventionally by using of bromine, a very toxic pollutant and hazard. In the last years several catalysts have been introduced but their regioselectivity is not high and require bromine for their preparation. The polyhalide (perbromide) ammonium salts have been used as brominating agents in mild conditions. These reagents can be used quantitatively in solid form, which facilitates their manipulation at laboratory scale. In the present communication a synthetic way for obtaining bromophenol derivatives using as brominating agent benzalkonium tribromide (**Benzal-Br3**) is reported. The reaction of phenolic substrates with Benzal-Br3 in dichloromethane-methanol mixture during 1–3 h at ambient temperature allows to obtain the corresponding bromoderivatives (>75%).

Keywords: benzalkonium chloride; quaternary ammonium polyhalides; bromination; phenols; bromophenols

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1. Introduction

Halogenation reactions constitute one of the most versatile and important chemical-industrial processes in contemporary industrial organic chemistry [1]. These reactions can be activated, under special conditions, by treatment with tert-butyl hypochlorite/hν or AIBN/heat [2] and tetraalkylammonium chloride/benzoyl peroxide/heat/CH3CN [3]. Some Fe (TPA)X2/TBHP and Mn (TPP)X/PhIO type metal complexes have been shown to participate in halogenation processes (chlorination and bromination) of organic substrates under phase transfer catalysis conditions [4].

The production of synthetic chemicals, flame retardants, disinfectants, bacteriostatic agents, insecticidal steroidal bromoderivatives, dyes, and antiviral drugs involves bromination processes [5,5a,5b]. Attempts to develop ecologically responsible bromination strategies with minimal environmental impact [6] currently focus on the action of halopeptidase enzymes, especially vanadium bromoperoxidase, but their prohibitive price and special conditions do not yet support their generalization on a laboratory scale [7,7a]. Jacobs et al. have tested the catalytic efficiency of basic lamellar solids (Mg-Al) impregnated with $WO4^{2-}$ under heterogeneous conditions for development of oxidative bromination of various organic substrates, using Br-/ H_2O_2 at room temperature [8]

Classical bromination in the aromatic core requires the use of highly polluting toxic dibromine (Br_2), which is difficult to handle and quantify, and catalysts such as $FeCl_3$, $FeBr_3$, I_2, thallium (III) acetate, generating undesirable byproducts [9,9ª]. In recent years new, more regioselective brominating agents [10,10a] have been developed and introduced into experimental practice, such as the Al_2O_3-Br_2 system for bromination of aromatic hydrocarbons, the dioxane-Br_2/SiO_2 system under microwave induction in the

absence of solvents, and the A-162 Br_2 type polymeric agents; but all require the use of dibromine (Br_2) for their preparation.

In order to achieve high regioselectivity in bromination reactions of aniline and derivatives, cationic surfactants and their molecular aggregates in aqueous suspensions have been attempted, but the yields do not exceed 75% [11]. Kojima et al. demonstrated the possibility of employing tetraalkylammonium halides (Cl-, Br-) and m-chloro perbenzoic acid in polar aprotic solvents to halogenate organic substrates [12]. Tamura et al. described the use of KH_3F_4/N- bromosuccinimide/CH_2Cl_2/room temperature system to obtain bromoderivatives with yields above 65% [13]. Roche et al. demonstrated the posibility of developing selective monobromination of deactivated anilines using KBr-$NaBO_3$ and catalytic amounts of ammonium or vanadium molybdate at room temperature [14].

Ammonium tribromide salts such as pyridinium tribromide, phenyltrimethylammonium tribromide, tetraalkylammonium tribromide [15,16] have been used as "mild" and selective brominating agents. Kajigaeschi has used polyhalogenated quaternary ammonium derivatives such as benzyltrimethylammonium chlorobromate and benzyltrimethylammonium tetra-chloroiodate to halogenate aromatic substrates (acetanilides and acetophenone derivatives) [17]. These reagents can be quantitatively employed in solid form, which facilitates their manipulation at laboratory scale [18]. Currently, the use of adamantane-type polyazamacrocycles and their polybromides as aromatic core-specific brominating agents has been reported with satisfactory yields [19].

The bromination of phenols and their derivatives has been widely reported, employing a variety of procedures [20]. However, the most widely used technique is the treatment with Br_2 in different solvents. This generates polybrominated byproducts which are difficult to separate and decrease the yield of the desired monoderivatives. In this field, the relevant work of Majetich et al. [21] should be highlighted, which uses bromodimethylsulfonium bromide generated in situ from HBr (47%) and dimethyl sulfoxide (DMSO) as a selective reagent in electrophilic aromatic bromination processes.

In the present communication we report the synthesis and characterization (FTIR and NMR) of benzalkonium tribromide (Benzal-Br_3), and a simple synthetic route for the efficient obtaining of bromo-derivatives from phenols, using Benzal-Br_3 as halogenating agent, which minimizes the use of Br_2 in organic solvents, the generation of polybromoderivatives, as well as decreases the pollutant load in laboratory conditions.

2. Materials and Methods

Melting temperatures were determined with Electrothermal 9100 capillary furnace equipment. FTIR spectra were analyzed on a Philips Analitical PU 9600 FTIR spectrophotometer (USA) in KBr pellets at 25 °C. The reagents, available from commercial firms Merck, BDH and Fluka, were used without prior purification. Benzalkonium chloride was used after recrystallization (twice) from ethanol-toluene-ether mixtures (2:1:0.5 *v*/*v*), being of pharmaceutical grade. All chemical-physical parameters of the products obtained were in concordance with those reported in the literature. The 13C- and 1H NMR spectra of the synthesized benzalkonium tribromide were recorded on a Bruker ACF-250 spectrometer (Dorstmund, Germany) at 238K operating at 62.50 and 250.13 MHz respectively. $(CD_3)_2SO$ (DMSO-d6) was used as solvent and TMS as internal standard. The chemical shifts were expressed in δ scale.

2.1. Benzalkonium Tribromide (Benzal-Br_3)

To a solution of benzalkonium chloride (19.55 g, 60 mmol) and sodium bromate (5 g, 32.8 mmol) in distilled water (100 mL) hydrochloric acid (47%, 180 mmol) is added slowly and dropwise under vigorous stirring (800–1200 rpm) at 5–10 °C for 35 min. The precipitated solid is extracted with dichloromethane (50 mL × 4). The organic phase (intense red color) is separated and dried with Magnesium sulfate ($MgSO_4$) and evaporated under vacuum to oil, which is recrystallized from a dichloromethane-ether mixture (10:1 *v*/*v*), for

obtaining an intense orange crystals. Tm, °C, 134–136. Yield 28 g, 88%. This polybrominated derivative is soluble in dichloromethane, dimethylsulfoxide, dimethylformamide and chloroform, being insoluble in n-hexane, benzene, CCl_4 and H_2O. FTIR (ν, cm^{-1}) 2815 (m, -N(CH_3)$_2$); 2790 (f, -N-CH_3); 2964, 1380 (s, -CH_3); 2926 (s, -CH_2-); 722 (w, -(CH_2)$_{7-9}$ -CH_3); 3060 (s, aromatic C-H); 1590 (m, skeletal C-C aromatic core vibrations); 1733, 1803, 1875, 1942 (m, typical overtone zone for C-H of monosubstituted aromatic derivatives). NMR-^{1}H. 7.40 (5H, m, aromatic protons); 4.39 (2H, s, CH_2-N); 3.11 (2H, m, N-CH_2-R); 2.82 (6H, s, 2CH_3-); 1.65-1.11 (22H, m, 11CH_2-); 0.70 (3H, t, R-CH_3).

2.2. Bromination Protocol with Benzalkonium Tribromide (Benzal-Br3)

All phenolic bromo-derivatives obtained are recrystallized from 1:3 *v*/*v* methanol-water mixture and their melting temperature (melting points) is determined by comparison with literature reports as well as by ^{1}H NMR.

2.3. Bromination of Phenol

To a phenol solution (1a) (0.50g, 5.31 mmol) in dichloromethane (30 mL)/methanol (20 mL) is gently added Benzal-Br3 (2.86 g, 5.40 mmol) at room temperature. After stirring for 40 min. the reaction mixture is discolored, allowed to stand for 5 min. and concentrated under reduced pressure. To the residue 20 mL of water are added. The mixture is extracted with ether (40 mL × 4). The ether phase is dried ($MgSO_4$) and concentrated to colorless needles. This crude product is recrystallized from methanol-water (1:3 *v*/*v*), yielding 0.85 g (93%) of 4-bromophenol (2a). Tm, °C, 61–63. NMR-1H (δ, ppm): 6.68 (m H-2; H-6); 7.18 (m H-3; H-5); 5.47 (-OH).

2.4. Bromination of 3,5-Dimethyl-Phenol

To a solution of 3,5-dimethyl-phenol (1k) (0.50 g, 4.09 mmol) in a dichloromethane (30 mL)/methanol (20 mL) mixture is added Benzal-Br3 (4.36 g, 8.23 mmol) at a temperature of 35 °C and under stirring (350 rpm). The reaction mixture is stirred for 35 min. until total decolorization of the solution. The solvent is distilled off and water (30 mL) is added to the residue obtained. The mixture is extracted with diethyl ether (40 mL × 4). The ethereal extract is dried over $MgSO_4$ and evaporated under vacuum to obtain a residue which is recrystallized from methanol-water (1:3 *v*/*v* 1.07 g (94%) of 2,4-dibromo-3,5-dimethylphenol is obtained. (2k) Tm. 73 °C

3. Results and Discussion

Commercial benzalkonium chloride, in the form of gelatinous plates, is a bacteriostatic agent widely used as an ophthalmic and local epidermal disinfectant. Its structure, a typical alkyldimethylbenzylammonium chloride, has been described since 1930s in different pharmacopoeias and pharmaceutical manuals [22,22a]. This derivative has not been used, nor its perbromide, previously, to obtain brominating agents from phenolic substrates. The reaction of benzalkonium chloride (Benzal-Cl) with bromine in dichloromethane generates Benzal-Br3, which can also be prepared by addition of hydrobromic acid (47%) to an aqueous solution of benzalkonium chloride and sodium bromate, obtaining satisfactory yields (88%), (Figure 1).

It is an orange solid, stable (6 months) to weathering and sunlight, non-hygroscopic and can be easily stored and handled under laboratory conditions. After a storage period of more than 7–8 months oxidative decomposition of this product is observed. Benzal-Br3 was characterized by ^{13}C and ^{1}H NMR and an approximation of its structural parameters was previously reported using the PM-323 calculation program. The reported spectroscopic data corroborate the proposed structure of this polybrominated quaternary ammonium salt. (Figure 2).

The reported spectroscopic data corroborate the proposed structure of this polybromi-nated quaternary ammonium salt. The integration of the ^{13}C NMR spectrum

and development of a DEPT experiment for complete signal assignment allowed us to corroborate the existence of 14 carbon atoms that constitute the alkyl chains present in Benzal-Br3. The presence of the Br_3^- anion of linear structure [24], causes a slight shift towards higher fields of the proton signals, as well as distortions in the bond angles of the nitrogen atom, deformations that can be explained due to steric repulsions and to the large volume of this linear anion. The ^{13}C chemical shift data for Benzal-Br3 are reported in Table 1.

$$PhCH_2NMe_2C_{11}H_{23}Br + Br_2 \rightarrow PhCH_2NMe_2C_{11}H_{23}Br_3$$

$$PhCH_2NMe_2C_{11}H_{23}\text{-}Cl + 1/2\ NaBrO_3 + 7/2\ HBr \rightarrow PhCH_2NMe_2C_{11}H_{23}Br_3 + 1/2\ NaCl + 1/2\ HCl + 1/2\ Br_2 + 3/2\ H_2O$$

Figure 1. General preparation of **BENZAL-Br3.**

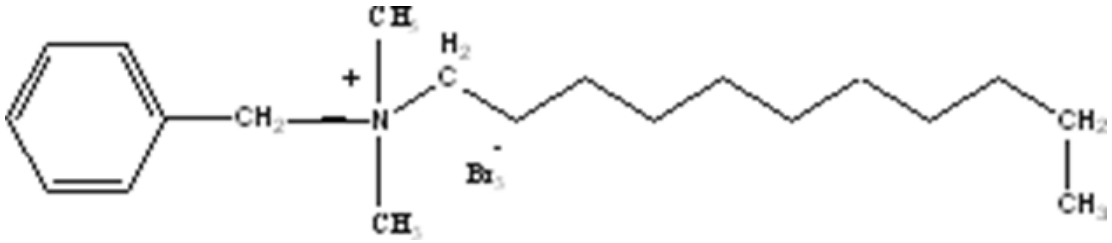

Figure 2. BENZAL-Br3.

Table 1. ^{13}C chemical shift data for **BENZAL-Br3.**

Chemical Shift, ppm, δ	Carbon Atom Assigned
132,9	C-3; C-5, aromatic core
130,3	C-1, aromatic core
128,9	C-2; C-6, aromatic core
128,1	C-4, aromatic core
69,8	CH2-X
66,2	Ar-CH2-N
63,5	N-CH2-R
49,2	CH3-N
31,3–21,8	-CH2-carbon chain
13,9	CH3-R-

Experimentally it is difficult to develop the bromination of phenols in the presence of Br_2, even operationally, it is required drop funnels with lateral pipelines to balance pressures, during the addition, in the reaction flask. The high reactivity of phenolic substrates leads to the practically quantitative formation of polybrominated derivatives. A known method of obtaining mono-bromophenols is the diazotization reaction of the corresponding substituted aromatic amines and subsequent heating in water. However, these methods require very long reaction times and tedious treatments of the reaction mixture. Of great synthetic significance is the development of a methodology that, varying only the molar ratios of the solid brominating agent (1 mol; 2 mol; 3 mol) and the substrate (1 mol), allows obtaining brominated derivatives with different degrees of substitution by Br in the aromatic core without affecting other functional groups. The use of solid brominating agents at room temperature, of easy manipulation, minimizes experimental risks and facilitates the treatment of the reaction mixture and the purification of the products.

The reaction of phenolic derivatives (1a–1l) with Benzal-Br3 in dichloromethane-methanol for 1–3 h at room temperature (25–40 °C) yields bromoderivatives (2a–2i). The results are summarized in Table 2. In the cases of preparation of 2,4,6- tribromophenol (2a); 2,4-dibromo-6-nitrophenol (2d) and 2,6-dibromo-4-nitrophenol (2e) calcium carbonate ($CaCO_3$) is added in order to neutralize the volumes of hydrogen bromide released during the halogenation process. The electrophilic bromination process of these phenolic substrates (1) can be considered to be completed when discoloration of the orange reaction mixture is detected, (Figure 3).

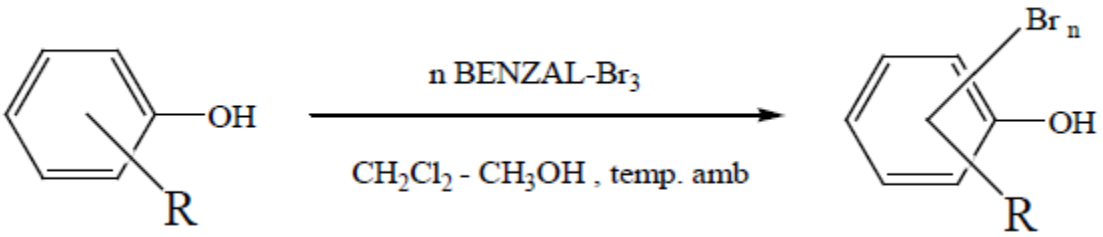

Figure 3. General schematic representation of bromination of phenol substrates with BENZAL-Br3.

Table 2. Bromination of phenols with benzalkonium perbromide BENZAL–Br3.

Substrate (1)	Products (2)		Molar Ratio Benzal-Br3:Substrate	Yield. %	Tm °C	Tm °C Lit.[25]
Phenol	2,4,6-tribromophenol	a	3:1 (2.89:1)	92	92	95
	2,4-dibromophenol		2:1	87	38–39	40
	4-bromophenol		1:1 (1.01:1)	93	61	63
4-methylphenol	2,6-dibromo-4-methylphenol	b	2:1 (1.78:1)	94	50	47
4-metoxyphenol	2,6-dibromo-4-metoxyphenol	c	2:1	91	84	---
2-nitrophenol	2,4-dibromo-6-nitrophenol	d	2:1	93	116	118
4-nitrophenol	2,6-dibromo-4-nitrophenol	e	2:1	89	144	144
1,4-dihydroxy-benzene	2,5-dibromo-1,4-dihydroxy-benzene	f	2:1	82	185	186
phloroglucinol	2,4,6-tribromo-phloroglucinol	g	3:1	93	154	152–153
α-naphtol	2,4-dibromo-1-naphtol	h	2:1 (2.12: 1)	90	107	105.5
			1:1	93	126	127–128
fenol	Oil mixture of products No reaction	i	no methanol 2:1	<6%	------	------
3,5-dimethyl-phenol	4-bromo-3,5-dimethyl-phenol	j	1:1 (1.009:1)	93	115–116	115–116
3,5-dimethyl-phenol	2,4-dibromo-3,5-dimethyl-phenol	k	2:1 (2.01: 1)	94	72	73
3,5-dimethyl-phenol	2,4,6-tribromo-3,5-dimethyl-phenol	l	3:1 (3.73: 1)	90	168	166

For obtaining monoderivatives (2a 1:1; 2h 1:1 and 2j 1:1) as can be observed when treating phenol (1a) and α-naphthol (1h) with molar amounts of Benzal-Br3 1:1 this brominating agent proves to be very useful, versatile, and easy to apply and allows to quantify more accurately the necessary amount of brominating agent at laboratory scale.

Using Benzal-Br3 as halogenating agent, the bromination process of 4-methoxyphenol is carried out in a single operation with yields above 85% (2c). The bromination of nitrophenols is simple and offers no operational risks. Polyhydroxybromobenzenes from

1,4-dihydroxybenzene (1f) and 1,3,5-trihydroxybenzene (1g) are easily prepared using this technique (2f, 2g). (2f, 2g).

4. Conclusions

The methodologically simple process of obtaining Benzal-Br3 tribromide does not require extreme conditions. It is emphasized that this technique for electrophilic bromination of phenols, using Benzal-Br3, synthesized from benzalconium chloride and sodium bromate-HBr, constitutes a useful method at laboratory scale due to its simplicity, ease of manipulation, operational safety and the excellent yields (80–93%) that are achieved, without the need to use expensive catalysts or conditions.

This brominating agent allows, via varying the Benzal-Br3: substrate molar ratio (1:1; 2:1; 3:1), to obtain selectively different brominated derivatives with satisfactory yields. This way of obtaining phenolic bromoderivatives can also be used in Organic Synthesis laboratory practices in undergraduate and graduate university teaching programs in order to develop an ecologically responsible vision by eliminating the use of molecular bromine.

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