Oxidation Using Quaternary Ammonium Polyhalides. IX.[1] Oxidation of Hindered Phenols with Benzyltrimethylammonium Tribromide

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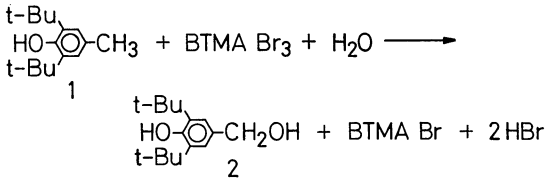
Synopsis. Reactions of hidered phenols, such as 2,6-di-*t*-butyl-4-methylphenol, 3,5-di-*t*-butyl-4-hydroxybenzyl alcohol, and 2,6-di-*t*-butylphenol, with benzyltrimethylammonium tribromide were carried out in dichloromethane in the presence of water, *t*-butyl alcohol, or aqueous sodium hydroxide at room temperature. Sequential reaction processes were provided by the obtained products.

Though the preparation of such hindered phenolic benzaldehyde as 3,5-di-*t*-butyl-4-hydroxybenzaldehyde by the usual methods is appreciably difficult, Coppinger el al. have already obtained this compound from a reaction of 2,6-di-*t*-butyl-4-methylphenol, with bromine in *t*-butyl alcohol.[2] In recent years we have found that benzyltrimethylammonium tribromide (BTMA Br_3) is a useful oxidizing agent.[3] In this paper we wish to report on the oxidation of hindered phenols by the use of BTMA Br_3, instead of bromine.

Results and Discussion

A reaction of 2,6-di-*t*-butyl-4-methylphenol (**1**) with an equimolar amount of BTMA Br_3 in dichloromethane in the presence of water at room temperature for 30 min gave 3,5-di-*t*-butyl-4-hydroxybenzyl alcohol (**2**) in quantitative yield. The reaction scheme can be represented as follows:



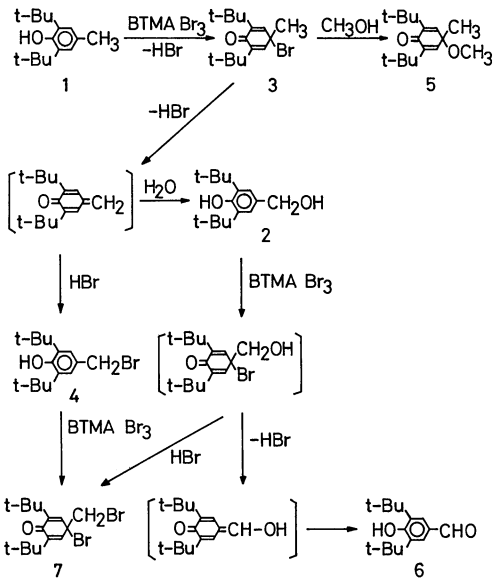
Scheme 1.

In this case, with only a 2-min reaction time, a mixture of **2** and 4-bromo-2,6-di-*t*-butyl-4-methyl-2,5-cyclohexadienone (**3**) was obtained. A mixture of **2** and **3** changed into a mixture of **2** and 4-bromomethyl-2,6-di-*t*-butylphenol (**4**) by a treatment with column chromatography on silica gel. Incidentally, the reaction of **1** with 1.0 equiv of BTMA Br_3 in methanol at 40 °C for 1 h gave 2,6-di-*t*-butyl-4-methoxy-4-methyl-2,5-cyclohexadienone (**5**) in good yield.

The reaction of **1** with 2.0 equiv of BTMA Br_3 and water in dichloromethane at room temperature for 3 h gave a mixture of 3,5-di-*t*-butyl-4-hydroxybenzaldehyde (**6**) and 4-bromo-4-bromomethyl-2,6-di-*t*-butyl-2,5-cyclohexadienone (**7**). In this case, when the reaction was carried out in the presence of *t*-butyl alcohol, compound **6** was obtained in satisfactory yield. Furthermore, when a large excess of BTMA Br_3 was used, compound **7** was obtained in quantitative yield.

The reaction of **2** with 1.0 equiv of BTMA Br_3 and water in dichloromethane at room temperature for 2 min gave a mixture of **6** and **7**. When the reaction of **2** with about 2 equiv of BTMA Br_3 was carried out for 1 h, compound **6** was obtained in good yield. That is, hindered phenolic benzaldehyde **6** was not oxidized into benzoic acid at room temperature, no matter how large was the excess of BTMA Br_3 used.[4]

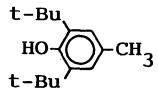
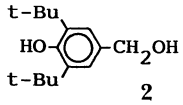
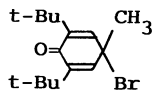
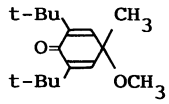
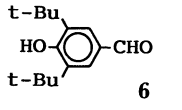
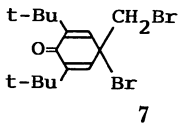
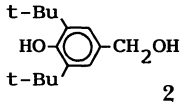
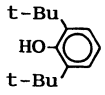
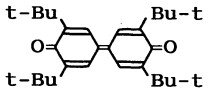
The results described above are summarized in Table 1; the products might be derived from **1** and **2** through the following sequential reactions:



Scheme 2.

We have previously reported that the reaction of several substituted benzyl alcohols with 1 equiv of BTMA Br_3 in carbon tetrachloride in the presence of water or aqueous sodium hydroxide gave the corresponding benzaldehydes.[3b] In these cases, the obtained benzaldehydes should have been derived by an elimination of the hydrogen bromide from benzyl

Table 1. Oxidation of Hindered Phenols with BTMA Br_3

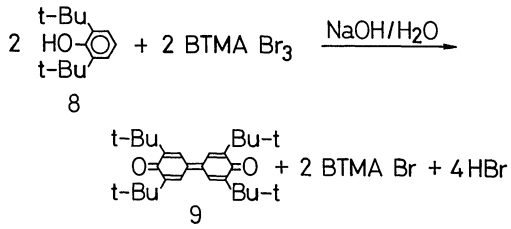
Run	Substrate	Molar ratio[a]	Solvent etc.	Reaction conditions		Product[b]	Yield[c]
				Temp/°C	Time		%
1	 **1**	1.0	CH_2Cl_2/H_2O	R.t.	30 min	 **2**	97
2[d]		1.0	CH_2Cl_2/H_2O	R.t.	2 min	**2**  **3**	—[e] —[e]
3		1.0	CH_3OH	40	1 h	 **5**	87
4[d]		2.0	CH_2Cl_2/H_2O	R.t.	3 h	 **6**  **7**	—[f] —[f]
5		2.0	CH_2Cl_2/H_2O/*t*-BuOH	R.t.	10 h	**6**	70
6		4.0	CH_2Cl_2/H_2O	R.t.	3 h	**7**	98
7[d]	 **2**	1.0	CH_2Cl_2/H_2O	R.t.	2 min	**6** **7**	—[g] —[g]
8		2.0	CH_2Cl_2/H_2O	R.t.	1 h	**6**	90
9	 **8**	1.0	CH_2Cl_2/H_2O/NaOH	R.t.	5 h	 **9**	61

a) BTMA Br_3/substrate. b) Products were characterized by comparing ^1H NMR spectra and mp with those of authentic samples or reported data. c) Yield of isolated product. d) Product was obtained as a mixture, and its ratio was determined by ^1H NMR spectrum. e) **2**/**3**=1/1. f) **6**/**7**=4/5. g) **6**/**7**=2/1.

hypobromites (R–C_6H_4–CH_2OBr), which are produced from benzyl alcohols with Br^+. However, in the reaction of **2** with BTMA Br_3, it is reasonable to consider that the reaction proceeded via an intermediate, 4-bromo-4-hydroxymethyl-2,6-di-*t*-butyl-2,5-cyclohexadienone, as shown in Scheme 2, since compound **7** is also obtain together with **6** when the reaction is run for a short time (Run 7). That is, compound **2**, a hindered phenolic benzyl alcohol, should first react with Br^+ at the 1-position, affording the intermediate.

Otherwise, it has already been reported that the reaction of 2,6-di-*t*-butylphenol (**8**) with oxygen in the presence of a base gives 3,5,3′,5′-tetra-*t*-butyl-4,4′-diphenoquinone (**9**).[5] This compound **9** has also been obtained by the oxidation of **6**, **8**, and 3,5-di-*t*-butyl-4-hydroxybenzoic acid with alkaline hexacyanoferrate (III) or lead dioxide in the absence of molecular oxygen.[6] We have now found that the reaction of **8** with 1.0 equiv of BTMA Br_3 in dichloromethane in the presence of aqueous sodium hydroxide at room temperature for 5 h gives **9** in satisfactory yield. This reaction may be included a dimerization of the corresponding phenoxyl radical.[6]

We believe that the main active species for oxidation in the presence of water is probably hypobromous acid, which may be produced from a reaction of



Scheme 3.

Scheme 4.

BTMA Br_3 with water. The oxidation of 1,4-benzenediols to 2,5-cyclohexadiene-1,4-diones with BTMA Br_3 in aqueous acetic acid was reported in our previous paper.[1] Similarly, it is almost certain that *t*-butyl hypobromite and sodium hypobromite are the main active oxidizing species for the reaction in *t*-butyl alcohol and in aqueous sodium hydroxide, respectively.

Furthermore, the reaction of phenols, which did not have a bulky *t*-butyl group at both *o*-positions for the hydroxyl group, with BTMA Br_3 gave electrophilic bromo-substituted products. For example, the reaction of 4-hydroxy-3-methoxybenzyl alcohol (vanillyl alcohol) with 1.0 equiv of BTMA Br_3 in dichloromethane in the presence of *t*-butyl alcohol gave 3-bromo-4-hydroxy-5-methoxybenzyl alcohol (60% yield).

We emphasize that the stable solid reagent BTMA Br_3 is a useful oxidizing agent for the hindered phenols, since it can be treated safely and quantitatively in comparison with toxic liquid bromine.

Experimental

Oxidation of 2,6-Di-*t*-butyl-4-methylphenol (1) with 1.0 equiv of BTMA Br_3 and Water (Table 1, Run 1): To a solution of BTMA Br_3 (1.17 g, 3.0 mmol) in dichloromethane (10 ml) was added **1** (0.66 g, 3.0 mmol) and water (10 ml). The mixture was stirred at room temperature for 30 min until the initial orange color faded. The water layer was then filtered through wet filter paper. The separated organic layer was washed with water and dried over $MgSO_4$, filtered, and evaporated in vacuo to give 3,5-di-*t*-butyl-4-hydroxybenzyl alcohol (**2**) as a yellow solid; yield 0.69 g (97%); mp 133—135 °C (lit,[2] mp 137.7—138.1 °C).

Oxidation of 1 with 1.0 equiv of BTMA Br_3 in Methanol (Table 1, Run 3): To a solution of **1** (0.66 g, 3.0 mmol) in methanol (30 ml) was added BTMA Br_3 (2.34 g, 6.0 mmol). The mixture was stirred for 1 h at 40 °C. After the reaction mixture was concentrated in vacuo, a yellow solid obtained was extracted with ether (10 ml×3), and the organic layer was evaporated in vacuo to give 2,6-di-*t*-butyl-4-methoxy-4-methyl-2,5-cyclohexadienone (**5**) as colorless needles; yield 0.29 g (87%); mp 95—97 °C (lit,[2] mp 94 °C).

Oxidation of 1 with 2.0 equiv of BTMA Br_3 and *t*-Butyl Alcohol-Water (Table 1, Run 5): To a solution of BTMA Br_3 (2.34 g, 6.0 mmol) in dichloromethane (10 ml) was added **1** (0.66 g, 3.0 mmol), water (10 ml) and *t*-butyl alcohol (10 ml). The mixture was stirred at room temperature for 10 h until the initial orange color faded completely. The mixture was then treated by a similar procedure to that described as Run 1. Thus, 3,5-di-*t*-butyl-4-hydroxybenzaldehyde (**6**) was obtained as colorless crystals; yield 0.49 g (70%); mp 191—193 °C (lit,[2] mp 189 °C).

Oxidation of 1 with Large Excess of BTMA Br_3 and Water (Table 1, Run 6): To a solution of BTMA Br_3 (4.68 g, 12 mmol) in dichloromethane (10 ml) was added **1** (0.66 g, 3.0 mmol), and water (20 ml). The mixture was stirred at room temperature for 3 h. The mixture was then treated by a similar procedure to that described as Run 1. Thus, 4-bromo-4-bromomethyl-2,6-di-*t*-butyl-2,5-cyclohexadienone (**7**) was obtained as yellow crystals; yield 1.11 g (98%); mp 132—134 °C (lit,[5] mp 118 °C). ^1H NMR ($CDCl_3$) δ=1.27 (18H, s, $2C_4H_9$), 3.96 (2H, s, CH_2Br), 6.61 (2H, s, Harom). Found: C, 48.74; H, 5.58%. Calcd for $C_{15}H_{22}OBr_2$: C, 47.64; H, 5.86%.

Oxidation of 3,5-Di-*t*-butyl-4-hydroxybenzyl Alcohol (2) with 2.0 equiv of BTMA Br_3 and Water (Table 1, Run 8): To a solution of BTMA Br_3 (2.34 g, 6.0 mmol) in dichloromethane (10 ml) was added **2** (0.71 g, 3.0 mmol) and water (10 ml). The mixture was then stirred at room temperature for 1 h. The mixture was treated as Run 1. Thus, compound **6** was obtained as colorless crystals; yield 0.63 g (90%); mp 191—193 °C.

Reaction of 2,6-Di-*t*-butylphenol (8) with 1.0 equiv of BTMA Br_3 and Aqueous Sodium Hydroxide (Table 1, Run 9): To a solution of BTMA Br_3 (1.17 g, 3.0 mmol) in dichloromethane (20 ml) was added **8** (0.62 g, 3.0 mmol) and aqueous sodium hydroxide (NaOH; 0.25 g, 6.3 mmol, H_2O; 14 ml). The mixture was stirred at room temperature for 5 h. The organic layer was then separated, washed with water, dried over $MgSO_4$, and evaporated in vacuo to give crude 3,5,3′,5′-tetra-*t*-butyl-4,4′-diphenoquinone (**9**) as a brown-red solid. The crude product was purified through a column packed with silica gel using hexane as a developing solvent. Thus, **9** was obtained as purple columnar crystals; yield 0.37 g (61%); mp 255—257 °C (lit,[5] mp 246 °C). IR (KBr) 1598 (C=O); ^1H NMR ($CDCl_3$) δ=1.35 (36H, s, 4 C_4H_9), 7.64 (4H, s, Harom). Found: C, 81.98; H, 10.21%. Calcd for $C_{28}H_{40}O_2$: C, 82.28; H, 9.89%.

References

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3) a) S. Kajigaeshi, K. Asano, S. Fujisaki, T. Kakinami, and T. Okamoto, *Chem. Lett.*, **1989**, 463; b) S. Kajigaeshi, T. Kakinami, T. Yamaguchi, T. Uesugi, and T. Okamoto, *Chem. Express*, **4**, 177 (1989); c) S. Kajigaeshi, H. Kawamukai, and S. Fujisaki, *Bull. Chem. Soc. Jpn.*, **62**, 2585 (1989); d) S. Kajigaeshi, K. Murakawa, K. Asano, S. Fujisaki, T. Kakinami, and T. Okamoto, *J. Chem. Soc., Perkin Trans., 1*, **1989**, 1702; e) S. Kajigaeshi, K. Murakawa, S. Fujisaki, and T. Kakinami, *Bull. Chem. Soc. Jpn.*, **62**, 3376 (1989); f) T. Okamoto, T. Uesugi, T. Kakinami, T. Utsunomiya, and S. Kajigaeshi, *Bull. Chem. Soc. Jpn.*, **62**, 3748 (1989).

4) We previously reported that the reaction of several substituted benzyl alcohols with 2 equiv of BTMA Br_3 in aqueous sodium hydroxide gave sodium benzoates in good yields.[3f]

5) M. S. Kharasch and B. S. Joshi, *J. Org. Chem.*, **22**, 1439 (1957).

6) C. D. Cook, E. S. English, and B. J. Wilson, *J. Org. Chem.*, **23**, 755 (1958).