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DIRECT CONVERSION OF AROMATIC 1,3-DIOXANES TO HYDROXYPROPYL ESTERS WITH PYRIDINIUM HYDROBROMIDE PERBROMIDE AND SODIUM ACETATE IN WATER

Shinsei Sayama*

Department of Chemistry, Fukushima Medical University, Hikarigaoka, Fukushima 960-1295, Japan; E-mail: pbtbw009@yahoo.co.jp

Abstract – Various aromatic 1,3-dioxanes were directly converted to respective hydorxypropyl esters with pyridinum hydrobromide perbromide and sodium acetate in water at room temperature.

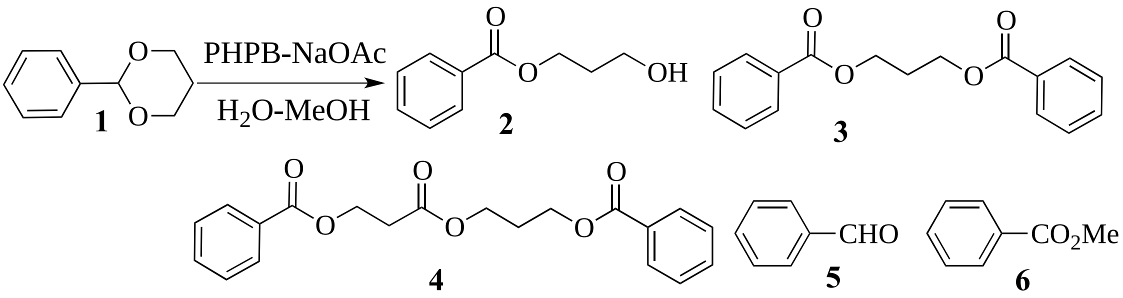
1,3-Dioxanes are widely used protective groups for carbonyl compounds and vicinal diols.[1] The oxidation of 1,3-dioxanes provides important hydoxypropyl esters for serving as cross-linking agents for polyesters and fungicides.[2] Direct conversion of open-chain acetals, dioxanes, and dioxolanes to corresponding esters can be mediated by a variety of reagents such as ozone, molecular oxygen-Co(II), hypochlorous acid, potassium permanganate, *N*-hydroxyphthalimide in electrochemical oxidation, and *tert*-butylhydroperoxide in the presence of Pd(II), Ru(III), or pyridinium dichromate (PDC).[3,4]

On the other hand, it was previously reported convenient oxidative methods for Tishchenko-like dimeric esterification of primary alcohols, esterification of aldehydes, and synthesis of oxazolines from aldehyde with commercially available pyridinium hydrobromide perbromide (PHPB) in water.[5] Therefore, the use of PHPB was expected to be attractive in other oxidative organic syntheses. It was seemed to be significant in finding a new procedure for oxidative conversion of dioxanes to hydroxypropyl esters with PHPB in water. We would like to report on the results of our studies concerning the direct conversion of aromatic dioxanes to hydroxypropyl esters with PHPB-NaOAc.

At first, the reaction of 2-phenyl-1,3-dioxane (**1**),[6] chosen as a representative aromatic 1,3-dioxane for this study, was carried out with various molar ratios of PHPB and NaOAc over **1** for obtaining hydroxypropyl benzoate (**2**). The results are summarized in Table 1.

At 1.0 molar ratio of PHPB over **1** in water at room temperature, hydoxypropyl benzoate **2** was afforded in 40% yield, accompanied by a mixture of diester (**3**), triester (**4**), and benzaldehyde (**5**) (run 1). At 2.0 molar ratio of PHPB over **1** the yield of **2** was not fully satisfactory, similarly accompanied by a mixture of diester **3**, triester **4**, and benzaldehyde **5** (run 2). It was assumed that deacetalization of **1** to **5** was

Table 1. Reaction of 2-phenyl-1,3-dioxane **1** with PHPB-NaOAc[a]



Run	PHPB	NaOAc	Solvent	Time (h)	Product, Yield (%) **2**	**3**	**4**	**5**	**6**	**1**
1	1.0	--	H_2O^a	21	40	40	4	11		--
2	2.0	--	H_2O^a	15	37	30	6	22		--
3	1.0	3.0	H_2O^a	22	86	--	--	8		--
4	1.0	3.0[c]	H_2O^a	23	56	--	--	39		--
5	2.0	3.0	H_2O^a	18	78	--	19	--		--
6	1.0	3.0	H_2O-MeOH[b]	20	89	--	--	6	--	trace
7	2.0	--	H_2O-MeOH[b]	24	56	--	--	17	22	--
8	2.0	3.0	H_2O-MeOH[b]	21	96	--	--	trace	--	--
9	2.0[d]	3.0	H_2O-MeOH[b]	24	63	--	--	20	13	--
10	2.0[e]	3.0	H_2O-MeOH[b]	24	--	--	--	9	--	86
11	2.0	6.0	H_2O-MeOH[b]	18	96	--	--	trace	--	--
12	--	3.0	H_2O-MeOH[b]	21	--	--	--	8	--	88

(PHPB and NaOAc: Molar ratio / **1**)

[a] **1**: 0.5 mmol; Solvent: H_2O (6 mL); Temp: rt. [b] H_2O (4 mL), MeOH (2 mL).
[c] NH_4OAc was used insted of NaOAc. [d] PTAB was used insted of PHPB.
[e] Pyridinium hydrobromide was used insted of PHPB.

caused in acidic conditions with HBr generated from PHPB in water. Esterification of benzaldehyde **5** and hydroxypropyl benzoate **2** took place to give diester **3** with PHPB in water as previously reported.[5b] The extent of this deacetalization to benzaldehyde **5** can be diminished by the addition of NaOAc for neutralizing the acidic conditions. The conversion of **1** to **2** with PHPB was carried out in the presence of

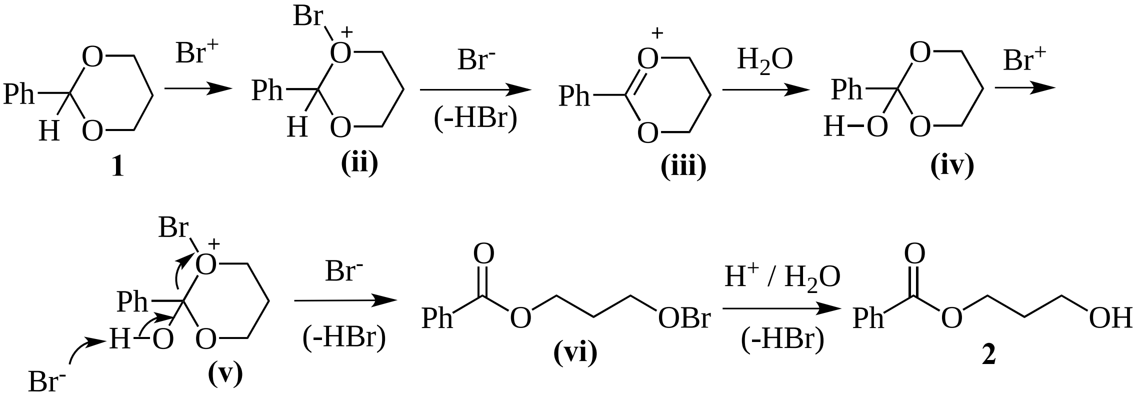
NaOAc to suppress deacetalization. At 1.0 molar ratio of PHPB and 3.0 molar ratio of NaOAc over **1**, hydroxypropyl benzoate **2** was expectedly obtained in moderate yield in water (run 3). The use of NH_4OAc instead of NaOAc in this method was not effective for conversion of dioxane **1** to hydroxypropyl ester **2** (run 4).

At 2.0 molar ratio of PHPB over **1** in the presence of 3.0 molar ratio of NaOAc, the mixture of benzoate **2** (78%) and triester **4** (19%) derived from Tishchenko-like dimeric esterification of **2**, was obtained (run 5).[5b] The production of Tishchenko-like dimeric ester **4** from **2** was seemed to be caused by overoxidation of **2** with excess amounts of PHPB over **1**. The mild oxidation of secondary alcohol was previously reported with trimethylphenylammonium tribromide (phenyltrimethylammonium tribromide, PTAB) in MeOH.[7] In H_2O and MeOH, the reaction of **1** was carried out with PHPB-NaOAc to reduce Tishchenko-like dimeric esterification of **2**. Hydroxypropyl ester **2** was expectedly afforded in good yield at 1.0 molar ratio of PHPB and 3.0 molar ratio of NaOAc in H_2O-MeOH without producing triester **4** (run 6). With PHPB in the absence of NaOAc, the yield of ester **2** was not fully satisfactory in H_2O-MeOH, accompanied by a mixture of benzaldehyde **5** and methylbenzoate (**6**) (run 7). At 2.0 molar ratio of PHPB and 3.0 molar ratio of NaOAc in H_2O-MeOH, hydroxypropyl ester **2** was afforded in 96% yield without generating diester **3**, triester **4**, benzaldehyde **5**, and methyl benzoate **6** (run 8). Accordingly, NaOAc and co-solvent MeOH were ascertained to suppress deacetalization of **1** and Tishchenko-like dimeric esterification of **2** respectively.

In addition, to examine the effect of PHPB the conversion of **1** to **2** was carried out with PTAB instead of PHPB in the presence of NaOAc in H_2O-MeOH.

The satisfactory yield of **2** was not observed at 2.0 molar ratio of PTAB and 3.0 molar ratio of NaOAc under the same reaction conditions (run 9). The reaction of **1** with pyridinium hydrobromide instead of PHPB took place to give recovered dioxane **1** (run 10). At 2.0 molar ratio of PHPB and 6.0 molar ratio of NaOAc over **1** in H_2O-MeOH, hydroxypropyl benzoate **2** was afforded in good yield (run 11). Even in the presence of excess amounts of NaOAc over dioxane **1** and PHPB, hydroxypropyl benzoate was found to be obtained and NaOAc was effective only for neutralizing the acidic conditions without generating by-products. Dioxane **1** was mainly recovered in the absence of PHPB (run 12). Consequently, the combination of PHPB and NaOAc in H_2O-MeOH was confirmed to be alternative direct procedure for conversion of 2-phenyl-1,3-dioxane **1** to hydroxypropyl benzoate **2**.

The above mentioned observations suggested that the conversion of 1,3-dioxane **1** to hydroxypropyl ester **2** with PHPB-NaOAc proceeded as follows illustrated in Scheme 1. First, the combination of PHPB and NaOAc appeared to generate Br^+, AcO^-, NaBr, and pyridinium hydrobromide. Then, oxygen of dioxane **1** was attacked by Br^+. Dehydrobromination of (ii) took place to give (iii) by Br^-. Hemiacetalization of (iii)



Scheme 1. Plausible reaction mechanism for 2-phenyl-1,3-dioxane **1** to 3-hydroxypropyl benzoate **2**

by H_2O produced intermediate (iv). Oxidative esterification step was proposed to enable for feasible route (iv → v → vi) in Scheme 1. Finally, hydroxypropyl ester **2** was produced by loss of Br^-.

To elucidate the limitations for this conversion of 1,3-dioxanes to hydroxypropyl esters, the reaction of various aromatic dioxanes was examined with PHPB-NaOAc under the same reaction conditions. The results of aromatic dioxanes are shown in Table 2.

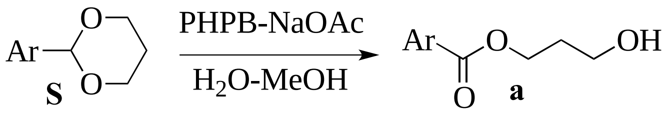
The reaction of 2-(2-chlorophenyl)-1,3-dioxane (**7**), 2-(3-chlorophenyl)-1,3-dioxane (**8**), and 2-(4-chlorophenyl)-1,3-dioxane (**9**) took place to give corresponding hydroxypropyl esters (**7a**), (**8a**), (**9a**) respectively (runs 1-3). 2-(2-Bromophenyl)-1,3-dioxane (**10**), 2-(3-bromophenyl)-1,3-dioxane (**11**), and 2-(4-bromophenyl)-1,3-dioxane (**12**) were similarly converted to hydoxypropyl esters (**10a**), (**11a**), (**12a**) in moderate yields (runs 4-6). In the present experiments the yields of **7a** and **10a** from 2-(2-chlorophenyl)-1,3-dioxane **7** and 2-(2-bromophenyl)-1,3-dioxane **10** possessing *ortho* halogen substitutent of aryl moieties, were not fully satisfactory, accompanied by 2-chlorobenzaldehyde or 2-bromobenzaldehyde. Deacetalization of **7**, **10** was seemed to proceed faster than that of conversion to hydroxypropyl esters to relieve the steric interaction between acetal and bulky halogen substituents on aryl moiety.

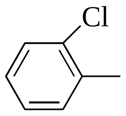
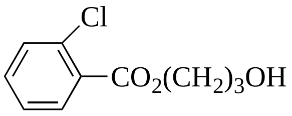
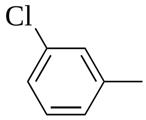
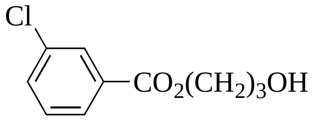
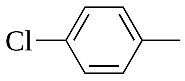
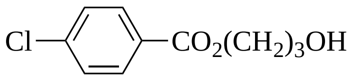
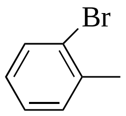
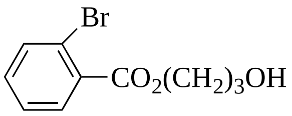
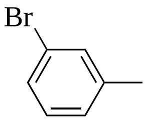
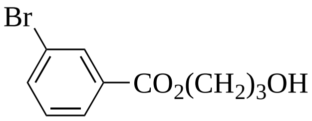
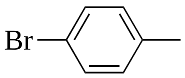
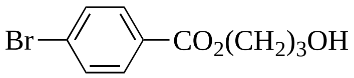
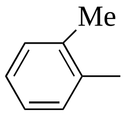
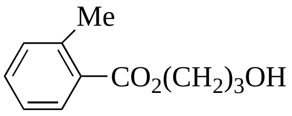
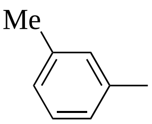
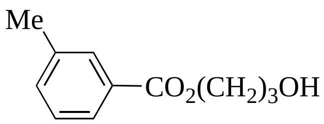
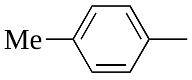
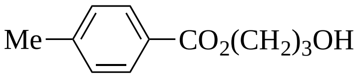
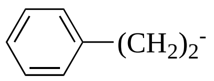
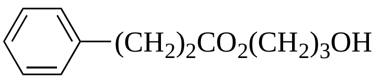
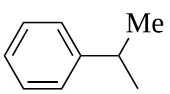
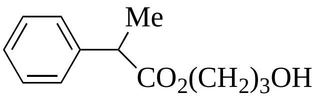
The reaction of *o*, *m*, *p*-toludioxanes (**13**), (**14**), (**15**) took place to give hydroxypropyl esters (**13a**), (**14a**), (**15a**) in moderate yields (runs 7-9). 2-(3-Phenylpropyl)-1,3-dioxane (**16**) and 2-(2-phenylpropyl)-1,3-dioxane (**17**) were also converted to corresponding esters (**16a**), (**17a**) in good yields (runs 10, 11).

The conversion of aromatic 1,3-dioxanes to hydroxypropyl esters by PHPB-NaOAc was not rested on electron donating or withdrawing substituents on aromatic ring.

As aromatic hydroxyl esters are of particular interest in the syntheses as cross-linking agents for polyesters and fungicides, the system PHPB-NaOAc in H_2O-MeOH provides an alternative oxidative method for conversion of 2-aryl-1,3-dioxanes to hydroxypropyl esters.[8]

Table 2. Reaction of aromatic dioxanes with PHPB-NaOAc[a]



Run	Substrate (**S**) Ar		Time (h)	Products		Yield (%)
1		**7**	24		**7a**	51[b]
2		**8**	17		**8a**	94
3		**9**	45		**9a**	83
4		**10**	24		**10a**	52[c]
5		**11**	19		**11a**	86
6		**12**	17		**12a**	87
7		**13**	17		**13a**	80
8		**14**	19		**14a**	84
9		**15**	19		**15a**	78
10		**16**	17		**16a**	93
11		**17**	17		**17a**	93

[a] **S**: 0.5 mmol; PHPB: 1.0 mmol; NaOAc: 1.5 mmol; H_2O: 4.0 mL; MeOH: 2.0 mL; Temp: rt. [b] 2-Chlorobenzaldehyde; 30%. [c] 2-Bromobenzaldehyde; 31%.

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8. Typical procedure: To a solution of 2-(4-methylphenyl)-1,3-dioxane (**15**, 89 mg, 0.5 mmol) and sodium acetate (204 mg, 1.5 mmol) in H_2O-MeOH (2:1 v/v, 6 mL), was added pyridinium hydrobromide perbromide (320 mg, 1.0 mmol) at room temperature. After stirring for 19 h at rt, the reaction mixture was treated with 0.5 M aq $Na_2S_2O_3$ (10 mL), 1.0 M aq $NaHCO_3$ (15 mL) and extracted with EtOAc (60 mL). The organic layer was washed with 0.5 M $Na_2S_2O_3$ and successively washed with saturated aq NaCl, and dried over $MgSO_4$. After removal of solvent in vacuo, the residue was purified by column chromatography on silica gel (Wako C-200) with CCl_4, CCl_4-$CHCl_3$ (2:1 v/v). Hydroxypropyl benzoate (**15a**, 76 mg, 0.39 mmol) was obtained in 78% yield. **15a**: IR (neat, cm^{-1}) 3419, 3036, 2959, 2888, 1715, 1612, 1577, 1509, 1455, 1407, 1389, 1310, 1277, 1208, 1178, 1112, 1052, 1020, 971, 927, 841, 754, 691, 637. ^1H NMR ($CDCl_3$) δ 2.00 (2H, m), 2.40 (3H, s), 3.77 (2H, t, *J*=6.2 Hz), 4.37 (2H, t, *J*=6.2 Hz), 7.25 (2H, d, *J*=7.8 Hz), 7.92 (2H, d, *J*=7.8 Hz). ^{13}C NMR ($CDCl_3$) δ 21.63, 31.93, 59.17, 61.56, 127.31, 129.09, 129.61, 143.73, 167.09. *Anal*. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.81; H 7.22.