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One-pot synthesis of ω-bromoesters from aromatic aldehydes and diols using pyridinium hydrobromide perbromide

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Abstract—A simple and efficient one-pot procedure has been developed for the synthesis of ω-bromoesters from aromatic aldehydes and diols in the presence of pyridinium hydrobromide perbromide (PHPB) and triethoxymethane in which aldehyde reacts first with diol and the product, cyclic acetal, reacts with PHPB to give the final product, ω-bromoesters.

In multistep synthesis, acetals, which are generally prepared by acid catalyst such as HCl,[1] $FeCl_3$,[2] Amberlyst-15,[3] $ZrCl_4$,[4] DDQ,[5] NBS,[6] $Bi(NO_3)_3$[7] and $[Hmim]BF_4$,[8] are well known as a protecting group of the carbonyl groups. Cyclic acetals are also used for the synthesis of ω-haloesters. For instance, Hanessian et al. have reported the conversion of cyclic acetals into the corresponding bromoesters using NBS.[9] This reaction is somewhat unique in that it allows a protection group to be converted into a reactive functionality. Similar conversions of cyclic acetals are also achieved by using NBS,[10] bromine[11] and bromotrichloromethane.[12] Ammonium tribromides such as pyridinium hydrobromide perbromide (PHPB) are generally used as an easy handle and useful brominating reagent instead of bromine. Recently, Patel et al. have reported an acetalization of carbonyl compounds using tetrabutylammonium tribromide (TBATB).[13] This procedure is very efficient and useful for the conversion of carbonyl compounds into acetals. The key step in this procedure is a generation of bromine from TBATB. Bromine can be used instead of TBATB for this reaction, and the acetals are also formed in good yield. However, bromine is hazardous and difficult to manipulate due to its toxicity and high vapor pressure. One-pot synthesis has attracted much interest in recent years because it provides a simple and efficient entry to compounds by including two or more transformations in a single operation to increase the complexity of a product starting from commercially available, relatively simple precursors. Herein, we report one-pot synthesis of ω-bromoesters from aromatic aldehydes and diols in the presence of PHPB as the brominating agent and triethoxymethane as the dehydrating agent. Quite recently, Sayama et al. have reported the esterification of aldehydes with alcohols in the presence of PHPB in water.[14] Using their conditions, the reaction with diols affords hydroxyesters. ω-Bromoesters are not formed.

ω-Bromoesters (**4**) were obtained in good yields by the reaction of aromatic aldehydes (**1**) with diols (**2**) in the presence of PHPB and triethoxymethane (see Table 1). For instance, a mixture of benzaldehyde (**1a**) (4 mmol), ethylene glycol (**2a**) (16 mmol), PHPB (8 mmol) and triethoxymethane (4.8 mmol) in dichloroethane (8 mL) was stirred for 2 h at 50 °C to give 2-bromoethyl benzoate (**4aa**) in 94% yield.[15] Large excess of PHPB and ethylene glycol were required to obtain the products in high yields. Among the brominating reagents tested, PHPB is the best one. NBS also gave **4aa** in 73% yield under the same conditions. Copper(II) bromide did not give **4aa**, but benzaldehyde ethylene acetal (**3aa**) was yielded in 60%. The reaction with bromotrichloromethane did not proceed, and **1a** was recovered quantitatively.

Several diols were used for this reaction (Table 2). The yields of ω-bromoesters (**4aa**–**ac**) decreased according to the increase of the alkyl chain length in the diols (**2a**–**c**). The reaction of **1a** with **2a** in the presence of

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Keywords: ω-Bromo esters; Pyridinium hydrobromide perbromide.

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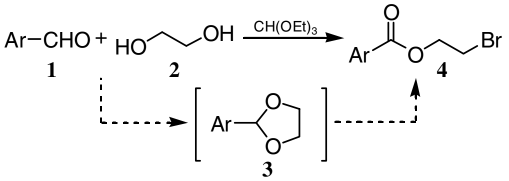
Table 1. Preparation of ω-bromoesters



Brominating reagent	Yield (%)
None	No reaction
PHPB	94
NBS	73
Copper(II) bromide	0 (60)[a]
Bromotrichloromethane	No reaction

[a] Yield of acetal.

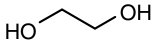
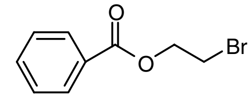
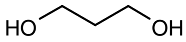
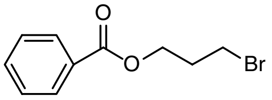
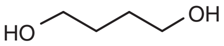
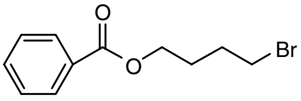
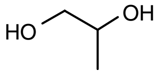
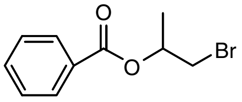
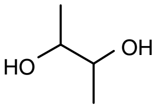
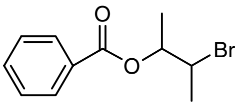
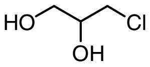
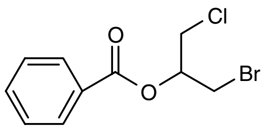
PHPB was smoothly proceeded to afford **4aa**, whereas the reaction with **2b** gave **4ab** in 70% yield along with a small amount of the corresponding acetal. The reactivity of **2c** was lower than that of **2a** under the same conditions, and trace amounts of **4ac** and the **3ac** were formed in the reaction with **2c**. β-diols (**2d–f**) also reacted with **1a** to give the corresponding ω-bromoesters (**4ad–af**) in good yields. The reactions with **2d** and **2f** gave **4ad** and **4af** along with a small amount of the regioisomer.

A series of aromatic aldehydes were used for this reaction (Table 3). Among monobromobenzaldehydes, the order of reactivity was *p* -> *m* -> *o*-bromobenzaldehyde; *o*-isomer is less reactive than *p*- and *m*-isomer. Compound **2a** reacted with *p*-isomer to give the bromoester **4da** in 81% yield, with *m*-isomer to give **4ea** in 61% yield, and with *o*-isomer to give **4fa** in 7% yield under similar conditions. Acetalization of *p*-nitrobenzaldehyde (**1g**) proceeded easily, but the bromoesterification of the resulting acetal proceeded very slow under the same conditions. However, the reaction of **1g** was carried out at 80 °C for 3 h to give **4ga** in 78% yield. Reaction of **2a** with terephthalaldehyde (**1h**) was carried out at 80 °C for 2 h to give **4ha** in 84% yield. 1- and 2-Naphthylaldehyde were also converted into the ω-bromoesters in excellent yields. The reaction of **2a** with 2-thiophenecarboxaldehyde (**1k**) did not afford the expected bromoester, and 5-bromo-2-formylthiophene (**5a**) was formed in 73% yield, in which the bromination of thiophene ring was prevailed over the acetalization. Resulting product, **5a**, was also inactive for acetalization.

When the reaction of **1k** with **2a** in the presence of large excess of PHPB was carried out at 80 °C for 3 h, 5-bromothiophene-2-carboxylic acid 2-bromoethyl ester (**5b**) was obtained in 39% yield. The reaction of aliphatic aldehyde such as hexanal gave a mixture of the desired bromoester and the α-brominated cyclic acetal (Scheme 1). These products could not be isolated from the reaction mixture, but they were confirmed by GC–MS, ^{1}H NMR and the spectral data shown in literature.[16]

The reaction of 4-methoxybenzaldehyde ethylene acetal (**3ca**) with PHPB gave the corresponding bromoester (**4ca**) in 52% yield along with 4-methoxybenzaldehyde (**1c**). In contrast, the reaction of **1c** with **2a** using our conditions afforded **4ca** in 92% yield, in which **3ca** was produced first, and then converted into **4ca** and starting

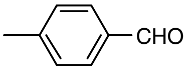
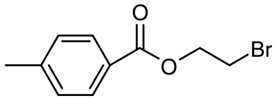
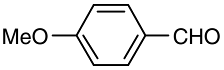
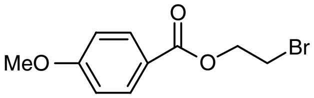
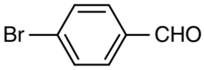
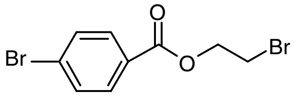
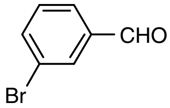
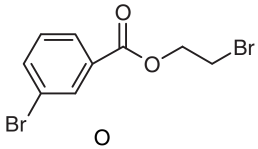
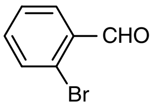
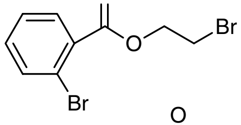
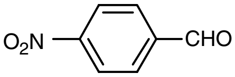
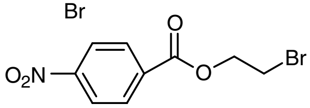
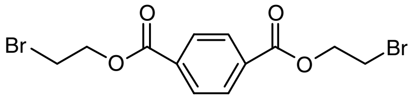
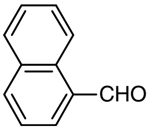
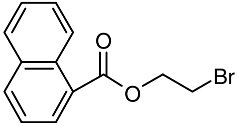
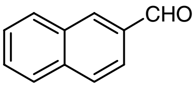
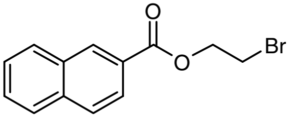
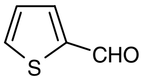
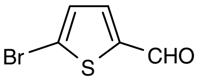
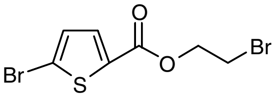
Table 2. Preparation of ω-bromoesters from diols and benzaldehyde

Diol		Product		Yield[a] (%)
2a		**4aa**		94
2b		**4ab**		70
2c		**4ac**		Trace
2d		**4ad**		87[b]
2e		**4ae**		89
2f		**4af**		68[b]

[a] Isolated yield.

[b] Contaminated with less than 6% of the regioisomer.

Table 3. Preparation of ω-bromoesters from ethylene glycol and various aldehydes

Aldehyde		Product		Yield[a] (%)
1b		**4ba**		97
1c		**4ca**		92
1d		**4da**		81
1e		**4ea**		61
1f		**4fa**		7 (45)[b]
1g		**4ga**		78[c]
1h		**4ha**		84[d]
1i		**4ia**		95
1j		**4ja**		95
1k		**5a**		73
		5b		39[e]

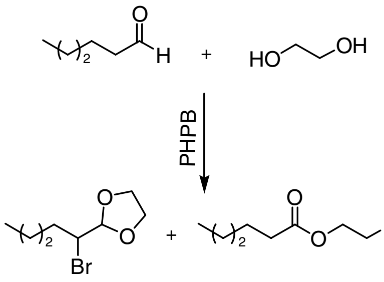
[a] Isolated yield.

[b] Parenthetic numbers indicate the yield of acetal.

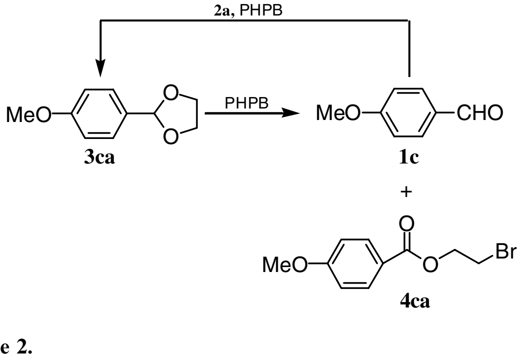
[c] 80 °C/3h.

[d] 80 °C/2h.

[e] 80 °C/3h, large excess of PHPB.



Scheme 1.



Scheme 2.

material, **1c**, which was converted to **3ca** again (see Scheme 2). Therefore the reaction completely proceeded to give **4ca** in excellent yield.

In conclusion, we have achieved an efficient method for the one-pot synthesis of ω-bromoesters from aromatic aldehydes and diols in the presence of PHPB. This reaction proceeded smoothly under mild conditions to give ω-bromoesters in high yields.

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15. General procedure: A mixture of aldehydes (4 mmol), diols (16 mmol), triethoxymethane (4.8 mmol) and pyridinium hydrobromide perbromide (8 mmol) in dichloroethane (8 mL) was stirred for 2 h at 50 °C. The reaction mixture was washed with aqueous sodium thiosulfate and aqueous sodium hydrogensulfite, and removed the solvent to give the crude product which was purified with column chromatography on silica gel.
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