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One-Pot Synthesis of ω-Bromoesters From Aromatic Aldehydes and Diols Using Phenyltrimethylammonium Tribromide

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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 phenyltrimethylammonium tribromide (PTAB) and (Diacetoxyiodo)benzene (DIB) in which aldehyde reacts first with diol and the product, cyclic acetal, reacts with acetyl bromide to give the final product, ω-bromoesters.

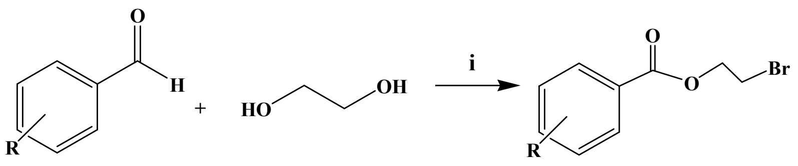
Keywords: ω-Bromo esters, hypervalent iodine, phenyltrimethylammonium tribromide.

Introduction

Bromoesters are valuable intermediates in organic synthesis. They could be employed as building blocks in organic, bioorganic, medicinal, and material chemistry [1]. In multistep synthesis, acetals, which are generally prepared by acid catalyst such as HCl, $FeCl_3$ [2], Amberlyst-15[3], $ZrCl_4$ [4]˒ DDQ [5], NBS [6] and $[Hmim]Br_3$ [7], are well known as a protecting group of the carbonyl groups. Cyclic acetyls 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. 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, bromine and bromotrichloromethane. Ammonium tribromides such as pyridinium hydrobromide perbromide (PHPB) [8] 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) [9]. 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. Quite recently, Sayama et al. have reported the esterification of aldehydes with alcohols in the presence of PHPB in water. Using their conditions, the reaction with diols affords hydroxyesters, ω -Bromoesters are not formed. 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. Few examples in details are given below.

Present work

As an alternative reagent to liquid bromine, organic ammonium tribromide such as PTAB, which is high molecular weight, stable, crystalline solid, is capable of delivering a stoichiometric amount of bromine where small amounts are necessary for micro scale reactions has been used. And also Diacetoxyiodobenzene (DIB), is a popular hypervalent iodine reagent, which is easy to handle, non-toxic,



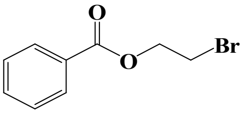
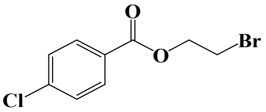
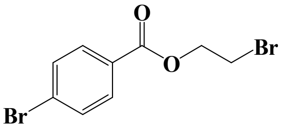
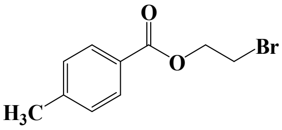
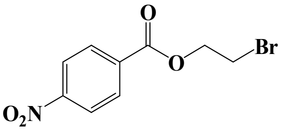
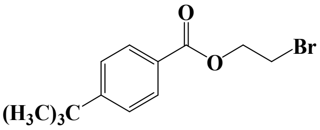
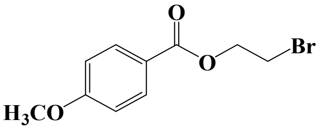
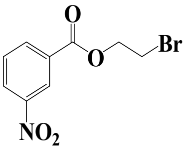
Scheme (1): PTAB/DIB

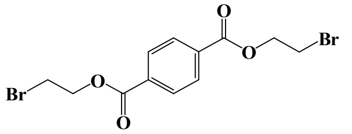
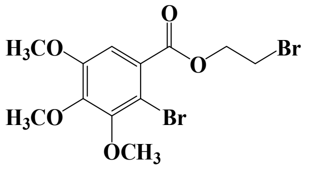
commercially available and is similar in reactivity to heavy metal reagents has been taken as dehydrating agent. In this work a novel application of PTAB for the one-pot synthesis of ω-bromoesters from aromatic aldehydes and diols has been demonstrated in (Scheme 1).

Experimental Section

A mixture of p-bromobenzaldehyde (2 mmol), ethylene glycol (4 mmol), DIB (4 mmol) and PTAB (4 mmol) in dichloroethane (8 mL) was added. The reaction mixture immediately turned to reddish, and was then subjected to stirring for 4 h at 50^0C. The progress of the reaction was monitored by TLC. After completion of the reaction, 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 (8: 1 petroleum ether/ethyl acetate).

Table (1): Bromoesterification of substituted aldehydes

Entry	R	Product	Time (h)	Yield %	M.P.(lit) ^{0} C
a	4-H		4	90	Liquid[8]
b	4-Cl		4	85	35(33-34)[10]
c	4-Br		4	85	57 (57-58)[8]
d	4-CH$_3$		4	90	Liquid[8]
e	4-NO$_2$		5	80	43(41-42) [8]
f	4-(CH$_3$)$_3$C		4	90	Liquid[8]
g	4-OCH$_3$		4	85	Liquid[11]
h	3-Br		4	80	Liquid[8]

i	4-CHO		4	80	97(96-97)[10]
j	3,4,5-$(OCH_3)_3$		4	70	Liquid[8]

Result and Discussion

The reaction of 4-chlorobenzaldehyde and ethane-1, 2-diol with PTAB and DIB in dichloromethane was chosen as model reaction. When PTAB was added to mixture of 4-chlorobenzaldehyde and ethane-1, 2-diol in CH_2Cl_2, the reaction mixture immediately turned to reddish, which slowly disappeared as the reaction progressed towards completion. The usual aqueous work-up of reaction mixture resulted in the formation of 2-bromoethyl 4-chlorobenzoate in 85% yield.

In a similar way, the reaction of ethylene glycol with a series of aromatic aldehydes containing different groups was investigated. The results were summarized in Table1.

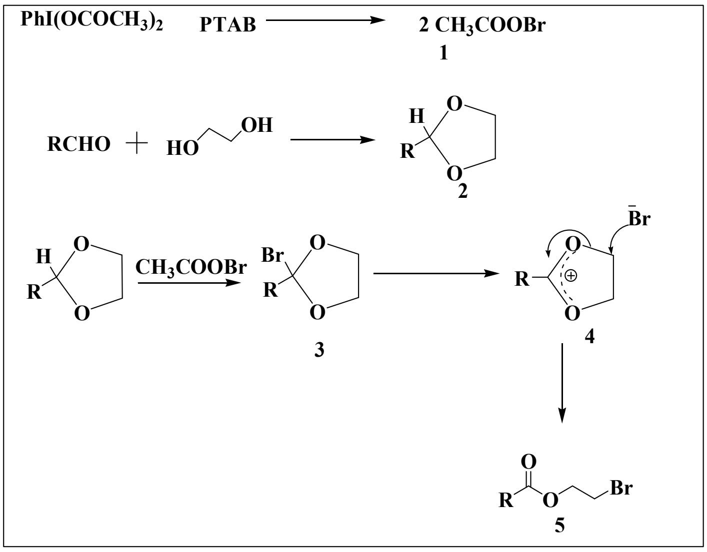
It was found that both electron-rich and electron-deficient aromatic aldehydes were suitable for this reaction, giving the desired products in good to excellent yields. For the electron-donating group such as methyl, tert-butyl, methoxy, and dimethoxy, the by-products of electrophilic aromatic bromination were not found (entries d, f and g). Unexpectedly, when 3, 4, 5-trimethoxy benzaldehyde was used for this reaction, the brominated product was obtained as the main product (entry j).

Reaction mechanism

The reasonable mechanism for bromo esterification of aldehydes and diols using DIB / PTAB in dichloromethane is shown in Scheme 6. The reaction is most readily rationalized by postulating initial formation of a 2-bromo-2-phenyldioxane **3** (dioxolane)[12] which then ionizes to the oxonium ion **4;** attack on **4** by the liberated bromide is supported by the observation that NBS bromination of *0,0'*-benzylidenecyclohexane-cis-l,2-diol gave the product of SN^2 attack, trans-2-bromocyclohexyl benzoate, after attack of bromine gives the bromoester **5.**

Conclusion

In summary, an efficient method for the facile conversion of aromatic aldehydes to bromoesters has been developed under mild conditions with high yields using PTAB in dichloromethane. This reagent avoids some of the difficulties associated with the use of liquid bromine, especially in the large scale reactions, such as toxicity, handling, troublesome work up procedures and the need to use an excess of oxidizing agent.



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