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LIPASE PS-C CATALYSED HYDROLYSIS OF ARYL DIESTERS: A NEW ROUTE TO THE SYNTHESIS OF ACHIRAL HALF ESTERS

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ABSTRACT: Pseudomonas cepacia lipase supported on ceramic particles (PS-C) offers a simple alternative route for the synthesis of achiral half esters, with very high yields, easy work up and remarkable substrate selectivity, as it cleaves only phenolic esters having a phenyl group (i.e. C_6H_5-O-CO-C_6H_5).

Suitably substituted polyhydric phenols are used as starting materials for the synthesis of natural polyphenolics viz. chalcones, flavones, isoflavones, coumarins, xanthones, catechins, etc. Selective protection and deprotection steps are often required to achieve the total synthesis of these compounds. The steps involved are rather difficult, moreover they increase the number of process and decrease the net yield thus making the overall synthesis quite cumbersome. Selectivity in enzyme mediated protection / deprotection of phenolic groups in polyhydroxy / polyacyloxy benzene derivatives, lacking a directly attached nuclear ketonic

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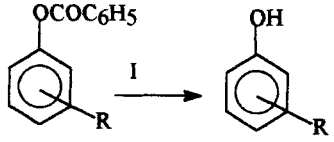
carbonyl group in dry solvents is not observed.[1] Generally, acid half-esters or half-esters are prepared by the esterification or interesterification with alcohols in the presence of acid catalyst,[2] by the hydrolysis of corresponding cyclic anhydride with alcohols [3] or by the hydrolysis of diesters by barium hydroxide.[4] Enzymatic hydrolysis of acid esters was carried out by using *pig liver esterase* to yield corresponding half esters.[5] By considering the importance of protection / deprotection in organic synthesis and the advantages of enzyme catalysis, we tried to incorporate lipase PS-C for the synthesis of achiral half esters.

In case of substrates **1(a-c)** deprotected products **2(a-c)** were obtained with high yields. Therefore lipase PS-C showed regioselectivity as selective monodeprotection of dibenzoyl esters was observed. After prolonged contact of the substrates with lipase PS-C, the parent phenols were formed. In order to study the substrate selectivity of this enzyme, hydrolysis of differently substituted esters of

Scheme-1

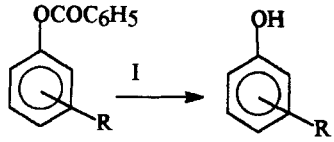


1(a-c) **2(a-c)**

R = -$OCOC_6H_5$;

ortho,meta, para.

Scheme-2

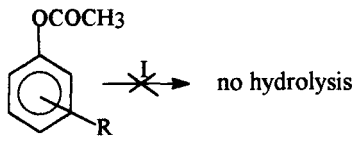


3(a-c) **4(a-c)**

R = -$OCOCH_3$;

ortho,meta, para.

Scheme-3

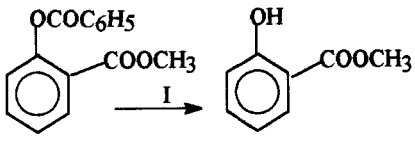


5(a-c) **5(a-c)**

R = -$OCOCH_3$;

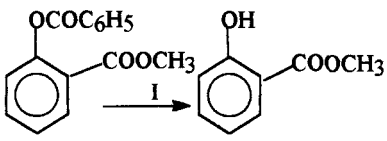
ortho,meta, para.

Scheme - 4



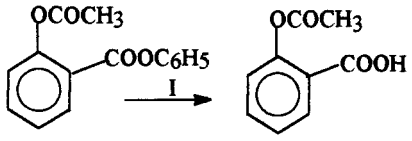
6 **7**

Scheme-5



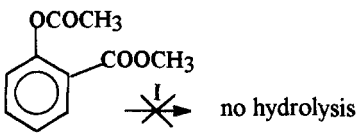
8 **9**

Scheme-6



10 **11**

Scheme-7



12 **12**

I = lipase PS-C/THF, phosphate buffer 0.1M pH 7

dihydric phenols **3(a-c)** were carried out. In this case only one product **4(a-c)** was formed with very high yield. Therefore it can be concluded that lipase PS-C selectively cleaves esters having phenyl group (i.e. -O-COC_6H_5) in the presence of acetyl group (i.e. -O-$COCH_3$). Both the analogies were confirmed, when substrates **5(a-c)** i.e. diacetyl esters of dihydric phenols did not undergo any hydrolysis. Finally we studied the effect of mixed esters (i.e. esters derived from phenols as well carboxylic acid esters). Substrates **6, 8** and **10** underwent hydrolysis to yield products **7, 9** and **11** respectively. From this it can be inferred that this enzyme shows remarkable regioselectivity as it hydrolysed only phenolic esters having phenyl substitutents and not carboxylic acid esters when R= methyl (i.e.-$COOCH_3$). The above inference was justified as compound **12** did not undergo enzymatic hydrolysis.

The regioselectivity and substrate specificity of lipase PS-C was further justified when control experiments using phenyl acetate and methyl benzoate were carried out. These substrates did undergo any hydrolysis reaction. In conclusion, lipase PS-C catalysed, the hydrolysis of diesters of phenols with remarkable regioselectivity and substrate selectivity. In the case of mixed esters (esters derived from both carboxylic acids and phenols) lipase PS-C selectively cleaved esters of phenols having phenyl substitutents with high yields and selectivity. The isolated products, their chemical yield and physical constant are summarised in the Table.

EXPERIMENTAL:

Products were confirmed by MP/ BP, IR and ^{1}H-NMR spectra. IR spectra were recorded using KBr pellets on Perkin-Elmer-738 spetrophotometer. ^{1}H-NMR

Table

Substrate	Product	Yield %	M.P/ BP (Literature)	Reaction time (hours)
1a	2a	85	63 (63-64)	7
1b	2b	83	135 (135-136)	6
1c	2c	91	163 (162-163)	4
3a	4a	89	58 (57-58)	5
3b	4b	88	282 (282 oil)	5
3c	4c	93	62 (62-63)	4
5a	5a	-	-	-
5b	5b	-	-	-
5c	5c	-	-	-
6	7	92	221 (221-224 oil)	7
8	9	93	158 (158-160)	8
10	11	-	138 (138-140)	7
12	12	-	-	-

spectra were recorded on Perkin-Elmer (300 MHz) spectrophotometer using $CDCl_3$ as a solvent and TMS as internal reference.

Preparation of aryl diesters was carried out using standard reported methods.[6] All the chemicals were of analytical grades and used without further purification. Pseudomonas cepacia supported on ceramic particles (PS-C) was obtained from Amano Pharmaceutical Company, Japan.

Enzymatic hydrolysis of aryl diesters :

The diester (250 mg) was dissolved in tetrahydrofuran. Lipase PS-C (50 mg) was added along with 5ml. of phosphate buffer (0.1M., pH 7) at room temperature. The reaction was kept for stirring and progress was monitored on TLC plates (coated with silica gel). The reaction was quenched by filtering off the enzyme through a celite pad. In case of schemes **1, 2** and **4** the filterate was washed with 1M. $NaHCO_3$ to remove the acid formed. The organic phase was then extracted with 0.1M NaOH solution. The aqueous layer was separated and products were reprecipitated by acidifying with 0.1M. HCl. In case of scheme **5** the organic phase was extracted with 1M. $NaHCO_3$. The aqueous phase was neutralised, filtered and the filterate was evaporated to dryness to compound **9**. In case of scheme **6** the organic phase was extracted with 1M. $NaHCO_3$. The aqueous phase was neutralised with 0.1M HCl to yield compound **10.**

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