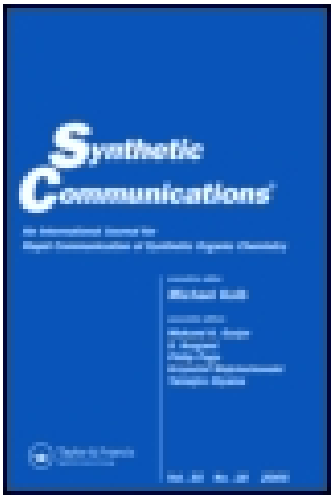

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Chemoselective Hydrolysis of Ester Bonds in the Presence of Baker's Yeast

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CHEMOSELECTIVE HYDROLYSIS OF ESTER BONDS IN THE PRESENCE OF BAKER'S YEAST

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The catalytic effect of baker's yeast on the hydrolysis of aliphatic esters in* p-*acetoxybenzoates is described. The chemoselective character of this reaction enables the selective protection of the hydroxyl group in* p-*hydroxybenzoic acid derivatives.

Keywords: Baker's yeast; ester hydrolysis; hydroxyl group protection

Biotransformations provide efficient procedures in organic synthesis because of the high selectivity of enzymes. Thus, the use of enzymes' labile protecting groups offers viable alternatives to chemical methods.[1] In this way, protection and deprotection can be carried out for polyfunctional molecules such as carbohydrates,[2] peptides,[3] nucleosides,[4] steroids, alkaloids, and phenolic natural products.[5]

Hydroxyl groups protected as esters of carboxylic acids can be liberated enzymatically. Many biocatalysts are used in this field, among them hydrolytic enzymes such as lipases, which are particularly suitable for the regioselective acylation and deacylation of primary and secondary hydroxyl groups.[6] In the deprotection of peracetylated phenols with broad spectrum of lipases in general, the sterically more accessible ones are cleaved.[5]

To explore new sources of hydrolases that display wider activities than those exhibited by commercially available enzymes, we screened microbial whole cells such as baker's yeast for hydrolytic activity.

The carbonyl group reduction is probably the most extensively studied baker's yeast–mediated biotransformation, but several hydrolytic enzymes (such as sterol ester hydrolase, carboxylic ester hydrolase, and lipase) have been isolated from *Saccharomyces cerevisiae*.[7,8] Their hydrolytic abilities, first discovered as an undesired side reaction,[9] were found to have an interesting application to the resolution of enantiomers of amino acids by submitting to hydrolysis of the *N*-acetyl derivatives of ethyl esters (Scheme 1).[6]

The hydrolysis reaction of racemic *N*-acetyl α-amino acids esters runs selectively in the ester group, but only derivatives of natural (*S*)-amino acids are subject to it. Enantiomer (*R*) can be regained in *N*-acetylamino ester form.[9]

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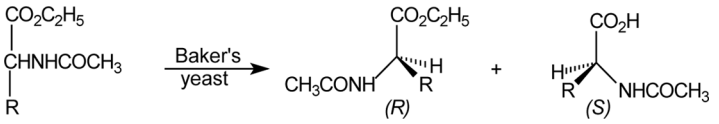


Scheme 1. Enantiospecific hydrolysis of amino acid esters.

Also, hydrolysis of racemic 1-alkyn-3-ol acetates[10] (Scheme 2) has led to the formation of the enantiomer, which is a major substrate in the synthesis of alkaloids, prostaglandins, pyrethroids, and steroids.

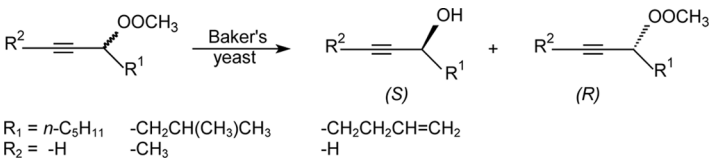
The aim of this study was to investigate the chemoselectivity in baker's yeast–mediated hydrolysis of esters of different carboxylic acids, especially aromatic and aliphatic esters. The comparison of the catalytic effect of baker's yeast on hydrolysis reaction of aliphatic and aromatic esters showed significant differences in the reactivity. Phenyl acetate underwent a complete hydrolysis during a few or several hours, depending on the reaction conditions (Scheme 3).

Interestingly, methyl benzoate did not exhibit any reactivity even after 3 days (Scheme 4).

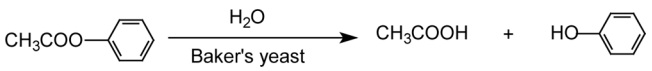
According to these observations, we have assumed that if a diester that comprises both aliphatic and aromatic ester groups undergoes hydrolysis, for example, methyl *p*-acetoxybenzoate, only hydrolysis of acetyl group will be possible, according to Scheme 5.

This hydrolysis reaction of methyl *p*-acetoxybenzoate was carried out, and the structures of the substrate and the obtained product were confirmed by infrared (IR) spectra. In the IR spectrum of the substrate, two characteristic stretching bands assigned to two ester groups were observed: 1731 cm^{-1} (acetate) and 1756 cm^{-1} (benzoate), whereas in the IR spectrum of the product only one band corresponding to the C=O– 1742 cm^{-1} group can be seen (benzoate). In the IR spectrum of the product, another band at 3428 cm^{-1} appears, which indicates the presence of an OH group formed in the course of the acetyl ester hydrolysis.

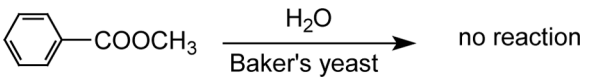
The kind of ester group of methyl *p*-acyloxybenzoate subjected to enzymatic hydrolysis depends on the enzyme applied: in the experiments using hydrolysis by commercially available pig liver esterase (PLE) and porcine pancreatic lipase (PPL), different selectivity of each hydrolase was observed.[11] Methyl *p*-acetoxybenzoate was hydrolyzed to hydroxyester in the presence of both



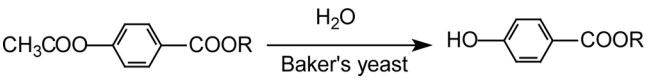
Scheme 2. Enantiospecific hydrolysis of 1-alkyn-3-ol acetates.



Scheme 3. Baker's yeast–assisted hydrolysis of phenyl acetate.



Scheme 4. Baker's yeast–assisted hydrolysis of methyl benzoate.

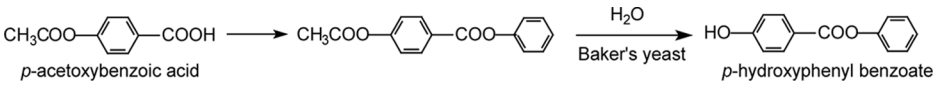


Scheme 5. Baker's yeast–assisted hydrolysis of methyl 4-acetoxybenzoate.

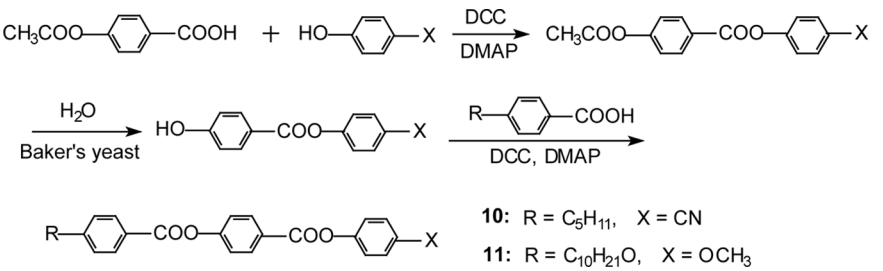
PLE and PPL (the only difference was the reaction rate), and hydrolysis of methyl *p*-benzoyloxybenzoate catalyzed by PLE gave only hydroxyester, whereas methyl *p*-nonanoyloxybenzoate in the presence of PPL gave nonanoyloxybenzoic acid.

The chemoselective character of the hydrolysis of acetoxybenzoates in the presence of baker's yeast means that it can be used in the selective protection of hydroxy groups in the derivatives of *p*-hydroxybenzoic acid. *p*-Hydroxybenzoic acid contains two functional groups, and to obtain its phenyl ester the hydroxy group should be protected to avoid side reactions. Esterification of the hydroxy group by acetic acid enables safe esterification of the carboxylic group into phenyl ester, and then after selective hydrolysis of the acetyl group it is possible to obtain hydroxyester (Scheme 6).

Phenyl 4,4′-substituted benzoates make an important group of liquid crystalline compounds,[12] and the method described may facilitate their synthesis. The described method was verified in the synthesis of 4-cyanophenyl 4′-[4″-(pentyl) benzoyloxy]benzoate (**10**) and 4-methoxyphenyl 4′-[4″-(decyloxy)benzoyloxy]benzoate (**11**), which is shown in Scheme 7.



Scheme 6. Synthesis of *p*-hydroxyphenyl benzoate.



Scheme 7. Synthesis of phenyl 4-benzoyloxybenzoates.

Table 1. Progress of the hydrolysis of some aromatic and aliphatic esters

No.	Ester	Substrate conversion (%)		
		4 h	24 h	48 h
1	Phenyl acetate	26	75	100
2	Phenyl heptanoate	15	52	100
3	Benzyl acetate	28	62	100
4	Benzyl propanoate	27	50	100
5	Ethyl pentanoate	47	88	100
6	Methyl benzoate	0	0	0
7	Ethyl benzoate	0	0	0
8	Phenyl benzoate	0	0	0
9	Benzyl benzoate	0	0	0

To confirm these observations on a broader group of compounds, we compared the catalytic effect of baker's yeast on the hydrolysis reaction of several different esters. The examined esters and the percentage out of them that underwent the reaction (detected by chromatography method) are shown in Table 1.

The obtained results have completely confirmed the initial observations: the progress of the reaction was in a strict correlation with the structure of the ester molecule.

- Only the hydrolysis of aliphatic esters of phenols or aliphatic alcohols in the presence of baker's yeast is possible.
- Among the examined esters, the fastest reaction rate was observed for aliphatic alcohol ester (ethyl pentanoate **5**); the elongation of the aliphatic chains in the carboxylic acid molecules inhibited the reaction rate.
- Benzoic acid esters did not show any reactivity under the applied conditions.

We compared our results with experiments performed without the addition of baker's yeast. After 2 days, the acetyl group was hydrolyzed about 15%; in the case of phenyl benzoate, we observed only traces of phenol after 3 days.

These experiments led us to the introduction of a convenient and inexpensive method for the protection of hydroxy groups in aromatic acids hydroxy esters.

EXPERIMENTAL

All the chemicals used were analytical-grade commercial products (Aldrich) and were applied without further purification. Esters from Table 1 were commercial products (Aldrich) or were synthesized according to known procedures.

The 4-methoxy- or 4-cyanophenyl esters of 4-acetoxybenzoic acid were prepared from the appropriate acids and phenols in the presence of *N,N′*-dicyclohexylcarbodiimide and a catalytic amount of *N,N′*-dimethyl-4-aminopyridine.

The IR spectra (in CH_2Cl_2) were recorded on a Perkin-Elmer 2000 apparatus equipped with Pegrams 2000 software, and the NMR spectra (in $CDCl_3$) were recorded using a Varian Gemini 200-MHz spectrometer. The structures were

confirmed also by elemental analysis (within ±0.4% of theoretical values). A purity of all compounds obtained was checked by means of thin-layer chromatography (TLC) using SiO_2 plates with ultraviolet (UV) indicator and chloroform as an eluent.

Hydrolysis reactions were carried out at room temperature in the presence of lyophilized baker's yeast (S. I. Lessafre) for 10 different esters. In the reaction, 3 g of Baker's yeast, 3 g of sucrose, 50 cm^3 of distilled water, and 0.0015 mol of a suitable ester dissolved in 0.5 cm^3 of ethanol were used. The samples of the reaction mixtures (chloroform extraction) were taken after 4, 24, and 48 h. The conversion percentage was identified with the aid of a Shimadzu GC-171 gas chromatograph using a BPX 70 capillary column and flame ionization detector.

Synthesis of 4-Methoxyphenyl 4-Hydroxybenzoate and 4-Cyanophenyl 4-Hydroxybenzoate with Baker's Yeast

A mixture of fresh baker's yeast (100 g) and sucrose (100 g) in distilled water (200 ml) was stirred for 15 min, after which an ethanolic solution (5 ml) of 4-methoxyphenyl 4′-acetoxybenzoate (3.4 g, 11.8 mmol) or 4-cyanophenyl 4′-acetoxybenzoate (1.8 g, 8.72 mmol) was added to it. The mixtures were stirred at room temperature for 5 days with TLC monitoring, and then 50 ml of chloroform were added to each of them and stirring was continued for another 24 h, after which the reaction mixtures were centrifuged. The supernatant was placed in a funnel, and the water phases were extracted with chloroform (2×50 ml). The collected organic phases were dried over $MgSO_4$, $CHCl_3$ was evaporated, and crude products were purified by column chromatography (SiO_2) using $CHCl_3$ as eluent to afford 1.5 g of pure 4-methoxyphenyl 4′-hydroxybenzoate (yield 52%) and 0.9 g of pure 4-cyanophenyl 4′-hydroxybenzoate (yield 43%).

Synthesis of 4-Cyanophenyl 4′-[4″-(Pentyl)benzoyloxy]benzoate (10) and 4-Methoxyphenyl 4′-[4″-(Decyloxy)benzoyloxy]-benzoate (11)

To 512 mg of 4-decyloxybenzoic acid (1.8 mmol) or 345 mg of 4-pentylbenzoic acid (1.8 mmol) dissolved in 30 ml of dry CH_2Cl_2, 450 mg of 4-methoxyphenyl 4′-hydroxybenzoate (1.8 mmol) or 430 mg of 4-cyanophenyl 4′-hydroxybenzoate (1.8 mmol) were added respectively. Next, 420 mg of N,N′-dicyclohexylcarbodiimide (DCC) (2 mmol) and a catalytic amount of *N,N*-dimethylaminopyridine (DMAP) were added to both mixtures. The reaction mixtures were vigorously stirred at room temperature for 24 h with TLC monitoring using $CHCl_3$ as eluent. The side product *N,N*′-dicyclohexylurea was filtered off and washed with CH_2Cl_2 (3×10 ml). Then, 20 ml of CH_3OH were added to both filtrates, which caused the products to precipitate from the mixture. The white solids were filtered off and washed with CH_3OH to afford 430 mg of pure 4-methoxyphenyl 4′-[4″-(decyloxy)benzoyloxy]benzoate (yield 48%; mps Cr 107 °C SmC 140 °C SmA 207 °C I) and 350 mg of pure 4-cyanophenyl 4′-[4″-(pentyl)benzoyloxy]benzoate (yield 50%; mps Cr 115 °C N 242 °C I).

^{1}H NMR data for **10** (200 MHz, $CDCl_3$, ppm): 0.907 (t, 3H, CH_3–, $J = 6.5$ Hz), 1.37 (m, 6H, –$CH_2CH_2CH_2$–), 2.71 (t, 2H, –CH_2Ph–, $J = 7.6$ Hz), aromatic protons:

7.32 (d, 2H, $J = 8.4$ Hz), 7.37 (d, 2H, $J = 8.6$ Hz), 7.42 (d, 2H, $J = 8.8$ Hz), 7.78 (d, 2H, $J = 8.8$ Hz), 8.14 (d, 2H, $J = 8.3$ Hz), 8.25 (d, 2H, $J = 8.8$ Hz).

^{1}H NMR data for **11** (200 MHz, $CDCl_3$, ppm): 0.88 (t, 3H, CH_3, $J = 6.8$ Hz), 1.28 [m, 14H, $-(CH_2)_7-$], 1.82 (m, 2H, $-CH_2CH_2O-$), 3.83 (s, 3H, $-OCH_3$), 4.05 (t, 2H, $-CH_2O$, $J = 6.6$ Hz), aromatic protons 6.94 (d, 2H, $J = 8.8$ Hz), 6.99 (d, 2H, $J = 8.4$ Hz), 7.14 (d, 2H, $J = 8.8$ Hz), 7.38 (d, 2H, $J = 8.8$ Hz), 8.17 (d, 2H, $J = 8.8$ Hz), 8.29 (d, 2H, $J = 8.6$ Hz).

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