# Oxime Esters as Novel Irreversible Acyl Transfer Agents for Lipase Catalysis in Organic Media

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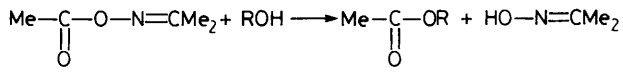
Oxime acetates and acrylates are established as efficient irreversible acyl transfer agents for lipase-catalysed transesterification in organic media.

Studies of enzyme function in non-aqueous media reveal new enzyme applications and provide insights into catalytic mechanisms.[1] Lipases have been extensively used to catalyse stereoselective transesterifications in organic media.[2] Our endeavour is to extend the lipase catalysed acylation methodology to prepare functionally substituted chiral and achiral acrylate monomers.

Lipase-catalysed transesterifications are often very slow due to the reversible nature of these reactions.[3] Our experiments reveal that reactions involving acrylate and methacrylate esters are even slower.† Recent investigations report the use of enol esters as irreversible acyl transfer agents where the leaving group, an unstable alcohol, tautomerizes to a ketone or aldehyde.[4]

Another way of displacing this equilibrium is to use substrate esters which liberate 'unreactive' hydroxy compounds. To check this new concept, we chose oxime esters (acetates and acrylates) which are analogous to enol esters and where the leaving group may not participate in the reverse reaction.

A simple representative experimental protocol for this biocatalytic transesterification reaction is as follows.[6] The substrate ester (20 mmol) (**1**—**6**) and the alcohol (20 mmol) (primary or secondary) in tetrahydrofuran (THF) (20 ml) was stirred at ambient temperature (~35 °C) with porcine pancreatic lipase (1 g) (PPL) (Sigma). Oxime acetates and acrylates were prepared by reacting acetyl chloride and




† We observed little change in the series methyl acrylate, ethyl acrylate, n-butyl acrylate, *etc.* There was no reaction between ethyl acrylate and secondary alcohol, *i.e.* cyclohexanol, even after 3 days.

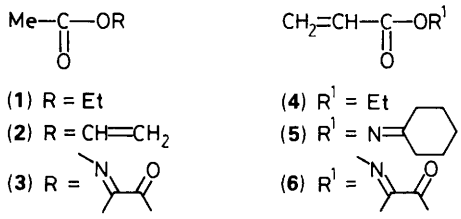



**Table 1.** Reaction of cyclohexanol with (**1**), (**2**), and (**3**) (1:1) in THF.[9]

| Time/h | (1)[b] | (2)[b] | (3)[b] |
|---|---|---|---|
| 2 | — | 3.87 | 9.44 |
| 4 | — | 8.16 | 16.51 |
| 6 | — | 9.09 | 22.92 |
| 24 | — | 23.17 | 51.92 |
| 48 | — | 29.34 | 57.52 |

[a] Lipase (1 g), THF (20 ml), 35 °C. [b] % Cyclohexyl acetate.

acryloyl chloride with biacetyl mono-oxime and cyclohexanone oxime respectively.‡

Our results demonstrate (Figures 1 and 2) that lipase displays an overwhelming preference towards oxime esters over alkyl or enol esters with n-butanol.§ Among the oxime esters, oxime acetate (over 90% after 6 h) (Figure 1) exhibits faster rates than the corresponding acrylate (80% after 48 h). Representative data in Table 1 indicates that the reactivities of esters follow the same trend with cyclohexanol but the differences are more pronounced. Reaction of racemic (±)-2-ethyl hexanol with (**5**) or (**6**) under similar conditions gave (+)-2-ethyl hexyl acetate, a commercial monomer, in its optically pure form [60% yield, 75% enantiomeric excess (e.e.)]. Examples of other chiral alcohols include (±)-menthol to give (+)-menthyl acrylate (65% yield, 90% e.e.) and (±)-2-ethyl hexane-1,3-diol to give (+)-2-ethyl 3-hydroxy n-hexyl acrylate (60% yield; $[\alpha]_D^{25}$ +8.33; *c* 1, benzene). Reaction of (±)-pentane-2,4-diol resulted in a mixture of products and total racemization. Geometrical isomers, *cis*- and *trans*-1,4-cyclohexane dimethanol, gave 50 and 20% monoester respectively with (**5**) after 12 h. The dramatic conversions with oxime acetates compared to even vinyl acetate underline the importance of reactant esters and suggest that the accelerated rates may not only be due to the suppression of the reverse reaction.

Control experiments with a 1:1 molar mixture of product ester (*i.e.* n-butyl acrylate) and oximes indicate no reaction even after 3 days. In earlier investigations similar control experiments could not be carried out with enol esters because of tautomerization.[7] The importance of selection of the substrate ester is further confirmed by the differences observed with the esters of two different oximes. We attribute this difference to the fact that the liberated diacetyl mono-oxime

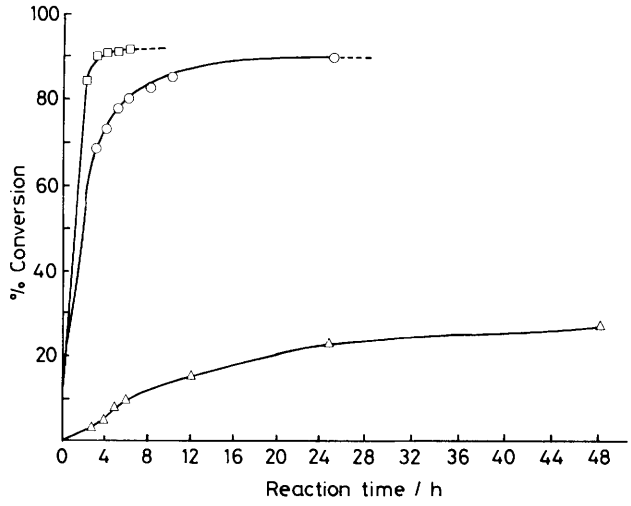



**Figure 1.** Lipase-catalysed reaction of acetate esters (**1**), (**2**), and (**3**) (20 mmol) with n-butanol (20 mmol) in THF (20 ml) at room temperature. △ ethyl acetate (**1**); ○ vinyl acetate (**2**); □ biacetyl mono-oxime acetate (**3**).

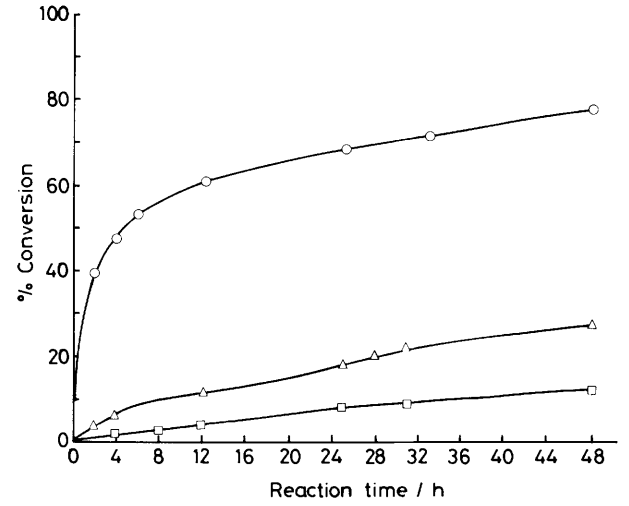



**Figure 2.** Lipase-catalysed reaction of acrylate esters (**4**), (**5**), and (**6**) (20 mmol each) with n-butanol (20 mmol) in THF (20 ml) at room temperature. □ ethyl acrylate (**4**) △ cyclohexanone oxime acrylate (**5**); ○ biacetyl mono-oxime acrylate (**6**). PPL (1 g) was used in each case.

forms six-membered intramolecular bonding and hence its ester exhibits faster rates of transesterifications. Taken together, these results fit into a straightforward chemical reactivity pattern and indicate that hydroxy and carboxy moieties can be varied to affect the rates of transesterification to a considerable degree.

Our work demonstrates a viable irreversible acylation methodology with exceptionally higher rates of transesterifications coupled with stereoselectivity and gives fresh impetus for preparing a variety of acrylate monomers by this biocatalytic process.

‡ The identities of oxime acetates and acrylates have been established by i.r. and n.m.r. spectroscopy. The purity and elemental compositions were verified by elemental analysis.

§ It is to be noted that enol ester methodology cannot be extended easily to prepare acrylate derivatives because of the difficulty in obtaining enol acrylates while oxime acrylates can be synthesized by a one-step procedure.

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