

## Diketene a New Esterification Reagent in the Enzyme-Aided Synthesis of Chiral Alcohols and Chiral Acetoacetic Acid Esters

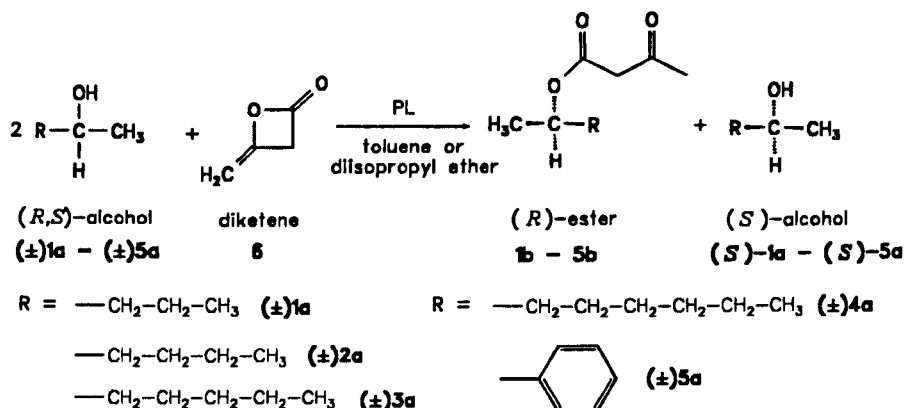
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**Abstract:** It was found that in the presence of *Pseudomonas* lipase diketene can be used as a new reagent for irreversible and enantioselective acylation of secondary alcohols. The reagent is useful to prepare optically active alcohols and optically active acetoacetic acid esters.

Since 1987 when de Jeso and Maillard et. al.<sup>1</sup> found that vinyl esters are suitable reagents in the enzyme-catalysed irreversible transesterification reactions of alcohols, numerous papers appeared in that highly interesting field of organic chemistry. In case of racemic alcohols, the transesterification is enantioselective<sup>2,3,4</sup> and in some cases the reactions could be improved by the application of vinyl laurate instead of vinyl acetate<sup>5</sup>. In our investigations of the applications of enzymes in organic syntheses, we found, that the reaction of diketene **6** with an alcohol rac. **1a-5a** can be catalysed at room temperature and in an organic solvent by the *Pseudomonas* sp. lipase (PL). Usually the reactions of diketene **6** with an alcohol are catalysed by a tertiary base or an alkoxide. To our knowledge the enzyme-catalysed reaction has not yet been reported. Moreover we found, that the reactions were enantioselective, if secondary alcohols rac. **1a-5a** were applied. In a control experiment without the enzyme we found that no or only a very slow reaction took place. Even after four days at room temperature, only traces of acetoacetic acid ester were detected. The reaction and the alcohols which we have used as some examples are shown in scheme 1. In contrast to the transesterification reaction with a vinyl ester, no by-product like acetaldehyde is produced. The reactions were carried out at room temperature in organic solvents like toluene or diisopropyl ether. Not suitable were alkanes like hexane, because the diketene **6** is not very soluble in them. The reaction took also place in pure diketene. After completion of the reactions, no diketene **6** was detected by GC any more. The stereochemistry of the products was the same as the one known from the transesterification reactions of the alcohols rac. **1a-5a** with the vinyl esters catalysed by *Pseudomonas* sp. lipase. This was determined by comparison with samples prepared from the rac. alcohols and vinyl laurate in the presence of *Pseudomonas* lipase<sup>5</sup>. The (*R*)-alcohols were faster acetoacetylated as the (*S*)-enantiomers. The enantiomeric excess depends on the residue R and the conversions. The results are listed in table 1. In each experiment a molar ratio of alcohol : diketene of 1 : 0.75 was applied.

Scheme 1

Table 1 Enantioselective esterification of secondary alcohols ( $\pm$ ) 1a-5a with diketene 6 catalysed by *Pseudomonas* lipase

(S)-alcohol	ee %*	yield%	(R)-ester	ee% **	yield %	$[\alpha]_D^{25}$ 1	$n_D^{20}$	b.p. (torr)	c %	E
(S)-1a	73	23	1b	31	62	-5.38	1.4265	47(0.5)	70	4
(S)-2a	96	61	2b	55	53	-5.87	1.4333	78(2.1)	64	12
(S)-3a	97	40	3b	42	47	-3.66	1.4347	94(3.5)	70	9
(S)-4a	95	77	4b	40	75	-3.19	1.4350	86(0.8)	70	8
(S)-5a	96	56	5b	54	59	+48.61	1.5047	115(2)	64	12

\*Determined by GC/chiral column FS-Cyclodex-beta-1/P (permethylated  $\beta$ -cyclodextrin, 50m, 0.25mm I.D.) (S)-1 to (S)-4 have been converted into the acetic acid esters.

\*\* Determined after hydrolyzation (MeOH/KOH) to the (R)-alcohols, and converted into the acetic acid esters, except (R)-5.

Because optically active acetoacetic acid esters have certain interest in the syntheses of pyrrolizidine alkaloids,<sup>6</sup> the preparation of enantiomerically pure compounds is under investigation. Since diketene is an easily available and cheap industrial chemical, the described reaction can be alternatively used instead of vinyl esters to prepare the optically active alcohols, or in addition to prepare the optically active acetoacetic acid esters.

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