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Tetrahedron Letters 45 (2004) 627–630
Tetrahedron Letters

On the use of succinic anhydride as acylating agent for practical resolution of aryl–alkyl alcohols through lipase-catalyzed acylation

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Received 27 August 2003; accepted 17 October 2003

Abstract—A comparison is carried out of the *E*-values recorded in the lipase-catalyzed resolution of a series of secondary aryl–alkyl alcohols with enol esters versus succinic anhydride. Whereas all the substrates could be resolved by a proper choice of the lipase/enol ester couple with moderate ($E = 50$) to good ($E > 100$) enantioselectivities, only some of them showed satisfactory enantioselectivity ($E > 50$) with the use of succinic acid as acylating agent. Notably, indanol and 1-quinolin-3-yl-ethanol were resolved in a practical way, with $E > 100$ and $E > 80$, respectively.

Enzymatic reactions have proved to be a convenient method for obtaining optically enriched compounds from their racemic form by kinetic resolution.[1] Notably, alcohols can be resolved through lipase-catalyzed transesterification (acylation) with enol esters in a—generally—irreversible reaction.[2] However, to be of preparative interest such a process requires (i) a high enantioselectivity factor *E*, (ii) easy separation of the unreacted substrate (alcohol) from the product (ester). The latter point is fulfilled in lipase-catalyzed hydrolysis of esters, for which the unreacted ester and the acid produced may be separated by a very convenient operation, that is a liquid–liquid extraction. This is not the case for transesterification or acylation processes, since alcohols and esters are both neutral compounds.

The use of a cyclic anhydride as an acylating agent may offer a convenient solution to this requirement.[3] Indeed, the acid–ester produced may be readily separated from the unreacted alcohol by a simple aqueous base–organic solvent liquid–liquid extraction. Moreover, since the separation of these compounds is easy even for very different amounts of product and unreacted substrate, alcohols of high enantiomeric purity may be obtained from a racemic substrate even in the cases of low *E* values, provided the acylation is carried out to high conversion.

We have described the use of succinic anhydride as an acylating agent for the resolution of substituted cyclobutylidenethanols.[4] An industrial application of such a process has been reported by Gutman.[5]

Since the structure of the intermediate acyl enzyme obtained by reaction of an enzyme with an acylating agent depends on the latter,[6] we were interested by the comparison of activity and enantioselectivity in the acylation of various substrates with 'standard' acylating agents such as vinyl or isopropenyl acetates on the one hand, and succinic anhydride on the other.

We thus investigated the lipase-catalyzed acylation of secondary benzylic alcohols **1**–**9** since these compounds may lead to biologically active compounds[7] or to α-arylpropionic acids.[8] Moreover, some are useful chiral synthons and substrates for palladium-catalyzed substitution reactions.[9]

Keywords: Alkyl–aryl secondary alcohols; Acylation; *Candida antarctica* lipase B (CAL B); *Pseudomonas fluorescens* lipase (PFL); Succinic anhydride.
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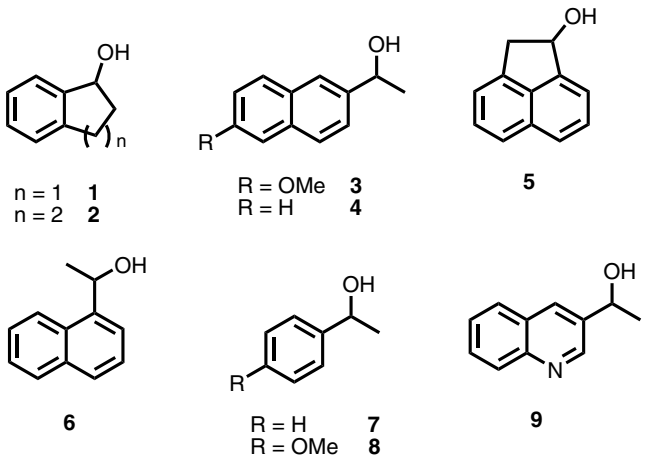
doi:10.1016/j.tetlet.2003.10.208



Compounds **1**, **4**, **5** and **7** were commercially available, whereas the other alcohols were obtained through borohydride reduction of the corresponding methyl ketone with the exception of **9**, which required a different synthetic procedure.[10]

Reactions were carried out using 2 mmol of racemic substrate dissolved in diethyl ether (10 mL). Vinyl or isopropenyl acetates (4 mmol, 2 equiv) or succinic anhydride (2 mmol), were then added, followed by the enzyme. Two commercially available lipases were used: *Pseudomonas fluorescens* lipase (PFL)[11] and *Candida antarctica* lipase B (CAL B),[12] an immobilized enzyme. The resulting mixture was stirred at room temperature for the appropriate time to reach approximately 50% conversion.

With enol esters as acylating agents, the unreacted alcohol and the acetate produced were separated by silica-gel flash chromatography. The ee's of both compounds could be measured before separation through analysis using chiral HPLC (Scheme 1).

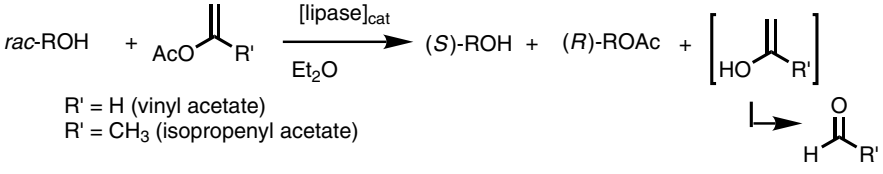
With succinic anhydride as acylating agent, the unreacted (*S*)-alcohol and the monosuccinate produced were separated by aqueous base–organic solvent liquid–liquid extraction. The aqueous phase was made alkaline with sodium hydroxide and the resulting (*R*)-alcohol extracted with an organic solvent (Scheme 2). Enantiomeric excesses of the unreacted (*S*)-enriched-alcohol and the (*R*)-enriched-alcohol produced were evaluated by chiral HPLC.

The results are collected in Tables 1 and 2 [acylations with vinyl acetate (VA) or isopropenyl acetate (IA)] and Tables 3 and 4 (acylations with succinic anhydride). With the exception of **9**, all the substrates could be resolved by suitable choice of the lipase/acylating agent couple, with moderate ($E = 40$) to good ($E > 100$) enantioselectivities. Generally, CAL B displayed better selectivities than PFL. They were often different according to the nature of the enol acetate, as expected.[6]

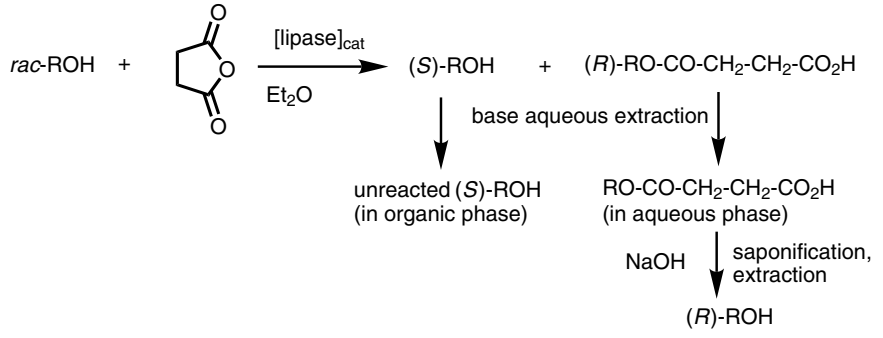
For the resolution of indanol **1**, the amount of lipase CAL B could be reduced from 300 to 25 mg and even 6 mg while keeping an enantioselectivity factor $E > 100$. The catalyst CAL B could be recovered and re-used up to seven times without a decrease in enantioselectivity ($E > 100$).

Acylations of acenaphthenol **5** and 2-(2-naphthyl)ethanol **4** also showed high selectivities, provided PFL ($E > 130$) was used for the former and CAL B ($E > 140$) for the latter.

E values recorded using succinic anhydride as the acylating agent were generally different from those measured



Scheme 1. Lipase-catalyzed acylation with enol acetates.



Scheme 2. Lipase-catalyzed acylation with succinic anhydride.

Table 1. CAL B-catalyzed acylation of alcohols **1**–**9** with enol esters

Substrate[a]	Enol ester	Conversion[b] (%)	Unreacted alcohol		Acetate produced		E[e]
			%Yield[c]	%Ee_s[d]	%Yield[c]	%Ee_s[d]	
1	IA	54	23	>99 (*S*)	29	85 (*R*)	60
1	VA	29	35	40 (*S*)	21	>99 (*R*)	300
2	IA	50	34	>99 (*S*)	32	>99 (*R*)	>1000
2	VA	53	34	>99 (*S*)	40	89 (*R*)	90
3	IA	50	42	>99 (*S*)	42	>99 (*R*)	>1000
3	VA	50	42	>99 (*S*)	43	99 (*R*)	750
4	IA	43	40	73 (*S*)	18	97 (*R*)	140
4	VA	50	26	96 (*S*)	28	97 (*R*)	260
5	IA	51	25	95 (*S*)	25	93 (*R*)	90
5	VA	26	18	34 (*S*)	18	97 (*R*)	90
6	IA	50	31	>99 (*S*)	31	>99 (*R*)	>1000
6	VA	50	33	>99 (*S*)	33	>99 (*R*)	>1000
7	IA	5	62	5 (*S*)	3	>99 (*R*)	40
7	VA	50	41	>99 (*S*)	37	>99 (*R*)	>1000
9	IA[f]	6	53	5 (−)	4	67 (+)	5

[a] 2 mmol in 10 mL diethyl ether; 22–24 h reaction time, unless otherwise stated. CAL B (300 mg).
[b] Determined from HPLC of the mixture on a Chiralcel® OD-H capillary column.
[c] After silica gel chromatography, hexane/ethyl acetate 80:20 (except for **9** 60:40).
[d] Determined by HPLC with a Chiralcel® OD-H capillary column, after acylation (Ac_2O, DMAP, NEt_3).
[e] Calculated from $E = \ln[(1-c)(1-ee_s)]/\ln[(1-c)(1+ee_s)]$.[13]
[f] 14 h reaction time.

Table 2. PFL-catalyzed acylation of alcohols **1**–**9** with enol esters

Substrate[a]	Enol ester	Conversion[b] (%)	Unreacted alcohol		Acetate produced		E[e]
			%Yield[c]	%Ee_s[d]	%Yield[c]	%Ee_s[d]	
1	IA[f]	53	40	>99 (*S*)	42	88 (*R*)	80
1	VA[f]	53	28	>99 (*S*)	19	87 (*R*)	70
2	IA[f]	50	32	>99 (*S*)	20	>99 (*R*)	>1000
2	VA[f]	51	32	>99 (*S*)	29	95 (*R*)	200
3	IA	13	72	15 (*S*)	11	>99 (*R*)	230
3	VA	34	42	51 (*S*)	33	>99 (*R*)	330
4	IA	12	52	13 (*S*)	7	96 (*R*)	56
4	VA	17	9	20 (*S*)	46	>99 (*R*)	240
5	IA	51	21	97 (*S*)	21	94 (*R*)	130
5	VA	32	26	47 (*S*)	26	99 (*R*)	310
6	IA[f]	—		—		—	
6	VA[f]	—		—		—	
7	IA	14	58	16 (*S*)	14	>99 (*R*)	130
7	VA	41	45	68 (*S*)	27	>99 (*R*)	190
8	IA[g]	23	59	29 (*S*)	22	>99 (*R*)	260

[a] 2 mmol in 10 mL diethyl ether; 22–24 h reaction time, unless otherwise stated; PFL (50 mg).
[b,c,d,e] See footnotes, Table 1.
[f] 48 h reaction time.
[g] 72 h reaction time.

Table 3. CAL B-catalyzed acylation of alcohols **1**–**9** with succinic anhydride

Substrate[a]	Conversion[b] (%)	Unreacted alcohol		Alcohol from ester saponification		E[e]
		%Yield[c]	%Ee_s[d]	%Yield[c]	%Ee_p[d]	
1	44	48	79 (*S*)	25	>99 (*R*)	480
2	46	47	79 (*S*)	30	91 (*R*)	50
3	60	38	69 (*S*)	13	47 (*R*)	6
4	43	46	81 (*S*)	38	96 (*R*)	110
5	18	60	15 (*S*)	12	67 (*R*)	6
6	<5		—	—		—
7	19	66	19 (*S*)	16	81 (*R*)	12
9	50[f]	31	92 (−)	31	92 (+)	85

[a,b,c,d,e] See footnotes, Table 1.
[f] 14 h reaction time.

Table 4. PFL-catalyzed acylation of alcohols **1**–**8** with succinic anhydride

Substrate[a]	Conversion[b] (%)	Unreacted alcohol		Alcohol from ester saponification		E[c]
		%Yield[d]	%Ee_s[e]	%Yield[d]	%Ee_p[e]	
1	30[f]	67	43 (*S*)	22	>99 (*R*)	300
2	48	30	78 (*S*)	37	86 (*R*)	30
3	45	50	62 (*S*)	14	75 (*R*)	13
4	15	58	13 (*S*)	11	73 (*R*)	7
5	51	32	97 (*S*)	27	93 (*R*)	110
6	<5[g]		—		—	—
7	15	58	16 (*S*)	12	85 (*R*)	15
8	35[h]		47 (*S*)		86 (*R*)	27

[a,b,c,d,e]See footnotes, Table 1.
[f]48 h reaction time.
[g]96 h reaction time.
[h]72 h reaction time.

with enol esters, either much lower (as for **3**) or higher (for **1**). Satisfactory enantioselectivities were recorded only for **1**, **2**, **4** and **5**. Under these conditions, enantiomers of *R* configuration were more reactive, and could be isolated from saponification of the succinic monoester collected in the alkaline aqueous phase. To our delight the system succinic anhydride/CAL B resolved 1-(3-quinolyl)ethanol **9** with higher activity and selectivity ($E = 85$) than IA/CAL B ($E = 5$ in a very slow reaction), and still better than the result we obtained previously ($E = 17$) using rabbit gastric lipase (RGL) as the catalyst.[14]

In conclusion, it has been shown that succinic anhydride can be used as an acylating agent in lipase-catalyzed kinetic resolution of benzylic-type alcohols. This procedure brings an improvement in the separation of the product from the unreacted substrate. This has been exemplified by a practical resolution of indanol and hitherto now unsatisfactory resolution of 1-quinolin-3-yl-ethanol.

Acknowledgements

Financial support by the 'Agence nationale pour la Recherche en Santé' (project no. 05/05/01/00 003) is gratefully acknowledged. The authors are grateful to Abdelkrim Boukhelouf and Amor Dehane for technical assistance.

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