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Utility of Acyloxypyridines and Acylazoles for the Lipase-catalyzed Enantioselective Acylation of 1-Phenylethanol

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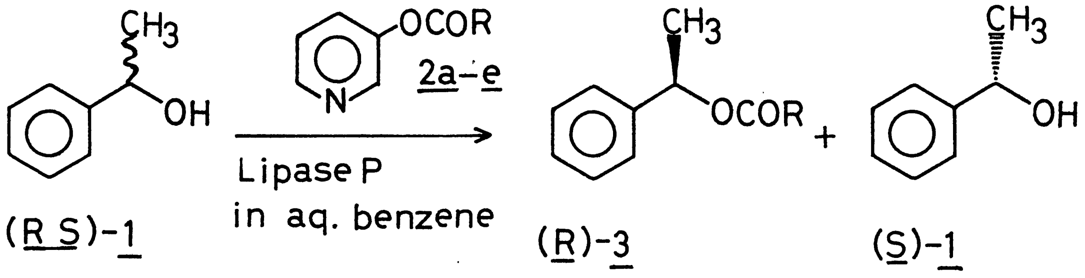
3-Acyloxypyridines and 4-acetyl-1,2,4-triazole were found to react enantioselectively with (RS)-1-phenylethanol to give (R)-1-phenethyl carboxylates in high purity, catalyzed by lipase P (from Pseudomonas fluorescens).

Hydrolytic enzymes have been exploited extensively as catalysts in asymmetric synthesis and resolution.1) Lipase-catalyzed esterification in organic solvents has attracted much attention to resolution of racemic alcohols.2) Esterification with carboxylic acids forms water to affect the thermodynamic equilibrium of the reaction.3) For overcoming this problem, a variety of acyl donors, such as activated esters,4) enol-esters,5) and carboxylic acid anhydrides,6) have been proposed thus far. However, these reagents possess some disadvantages. Reactive species resulted from acyl donors after reaction gives side reactions and/or affects on the yield of esters.4a) Little attention has been paid to the nitrogen-containing heteroaromatic acyl donors, in spite of great interest in that they may have an affinity toward enzymes and generate a neutral species after the reaction. In this paper, we wish to report the utility of acyloxypyridines (2a-h) and N-acylazoles (2i-k) for the enantioselective acylation of racemic 1-phenylethanol (1) catalyzed by lipase Amano P (from Pseudomonas fluorescens).7)



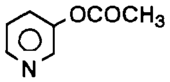
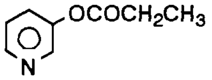
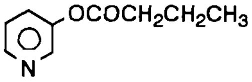
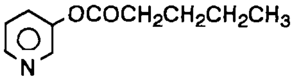
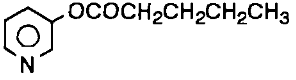
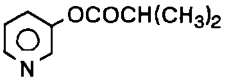
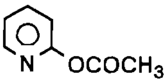
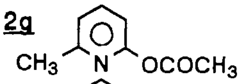
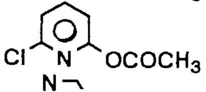
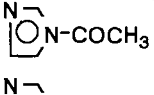
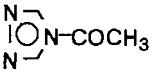
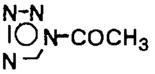
Results for the enantioselective acylations are summarized in Table 1. A typical experimental procedure is described for the entry with 2a. Compound 2a (1.27 g, 8.2 mmol) was stirred with lipase Amano P (0.06 g supported on 0.24 g of Celite, No 545 from Johns-Manville) in water-saturated benzene (10 ml) for 1 h at 20 °C. To the magnetically stirred mixture was added a solution of (RS)-1-phenylethanol (1.00 g, 8.2 mmol) in benzene (5 ml), and the reaction mixture was stirred for 10 h at 20 °C. The immobilized lipase was filtered off and washed with ether (ca. 50 ml). The combined organic layer was washed with water (30 ml x 3), dried over anhyd. sodium sulfate, and evaporated to dryness. Chromatography on silica gel with 90:10 hexane/ether as an eluant afforded 0.62 g (45% yield) of (R)-(+)-1-phenethyl acetate $[\alpha]_D^{24}$ +100° (c 1.5, cyclopentane) (99% ee) and 0.50 g (50% yield) of (S)-(-)-1-phenylethanol $[\alpha]_D^{24}$ -46.5° (c 1.0, cyclopentane)(85% ee).

Other results were obtained by a similar procedure to 2a.

We carried out also the acetylation with acetic anhydride under this condition in order to compare with our reagents, since acetic anhydride had been reported to be the best reagent for the enantioselective acylation of 1.6a)

As shown in Table 1, compounds 2a, 2g, and 2j acetylated successfully the (R)-form of 1 to give (R)-(+)-1-phenethyl acetate in quite high yields and high purity. The remaining alcohol was recovered as the (S)-form in high optical purity. The yield and the enantiomeric excess of the obtained

Table 1. Results of the acylation of (RS)-1-phenylethanol with acyloxypyridines and N-acetylazoles catalyzed by lipase P

Run		Acyl donor	Solvent[a] Time / h	Isolated products 3 Yield / %[b]	 ee / %[c]	 1 Yield / %	 ee / %[i]
1	2a		Benzene 10	45	99 (R)[d]	50	85 (S)
2	2b		Benzene 10	40	95 (R)[e]	45	94 (S)
3	2c		Hexane 10	37	99 (R)[f]	33	69 (S)
4	2d		Hexane 10	31	99 (R)[g]	---[j]	
5	2d		Hexane 24	46	99 (R)[g]	---[j]	
6	2e		Benzene 10	3	99 (R)[h]	---[j]	
7	2f		Benzene 10	50	81 (R)[d]	30	99 (S)
8	2g		Benzene 10	50	99 (R)[d]	41	98 (S)
9	2h		Benzene 10	47	84 (R)[d]	17	68 (S)
10	2i		Benzene 10	20	36 (R)[d]	12	57 (S)
11	2j		Benzene 10	47	99 (R)[d]	51	92 (S)
12	2k		Benzene 10	10	4 (R)[d]	74	0.4 (S)
13		$(CH_3CO)_2O$	Benzene 10	34	82 (R)[d]	50	62 (S)

a) Water-saturated solvents were used. b) The chemical purity of products were determined by the HPLC and ^{1}H NMR. c) The ee values were determined on the basis of the comparison of the observed $[\alpha]_D$ with those of chemically synthesized, optically pure authentic compounds. d) Based on $[\alpha]_D^{24}$ +101.2° (c 1.5, cyclopentane), $[\alpha]_D^{24}$ +121.6° (neat), Lit.[8] $[\alpha]_D$ +121.3° (neat). e) Based on $[\alpha]_D^{24}$ +112.6° (c 1.0, cyclopentane). f) Based on $[\alpha]_D^{24}$ +87.2° (c 1.1, cyclopentane). g) Based on $[\alpha]_D^{24}$ +79.4° (c 1.2, cyclopentane), Lit.[9] $[\alpha]_D^{25}$ +42.3° (neat). h) Based on $[\alpha]_D^{24}$ +94.5° (c 1.0, cyclopentane). i) Based on $[\alpha]_D^{24}$ -54.7° (c 1.0, cyclopentane), Lit.[6a] $[\alpha]_D^{20}$ -47.0° (c 2.2, hexane). j) Isolation by the chromatography was unsuccessful because of the contamination by the acylating reagent.

acetate are much higher than those with acetic anhydride. However, compounds **2i** and **2k** showed low reactivity and poor enantioselectivity toward the acetylation of **1**. The other acylation of **1** has been also proved to be effective in the reaction system with **2b**-**e** containing propionyl, butyryl, isobutyryl, and valeryl groups as the acyl group, although the reaction rates decrease with increase in the chain length of acyl group. The yields of esters can be improved by the duration of reaction (runs 4 and 5).

Consequently, we believe that 3-acyloxypyridines are effective for the enantioselective acylation of **1** with the lipase catalyst.

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