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Synthesis of α-Arylthioalkyl Esters: The Addition Reactions of Vinyl Esters with Arylthiols Catalyzed by Lipase

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α-Arylthioalkyl esters can be prepared by the addition reactions of vinyl esters with arylthiols in the presence of Pseudomonas lipase (PSL) as catalyst. In the toluene, the reaction mixtures were stirred at 60 °C for three days, the chemical yields up to 85% were obtained.

INTRODUCTION

α-Arylthioalkyl esters **3** are very important intermediate in organic synthesis. When these compounds are treated with tributyltin hydride, radical intermediates are generated which might undergo many reactions. Radical reaction has been applied to natural product synthesis.[1] As a bifunctional compounds, the esters can react with nucleophiles in the presence of tin(IV) chloride to provide a convenient method for carbon-carbon bond formation.[2]

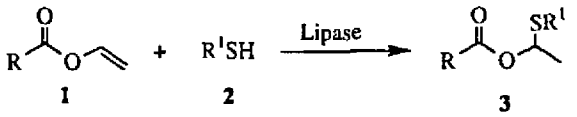
In the past few years, α-arylthioalkyl esters have been prepared by Pummmerer reaction,[3] alkylation of the corresponding carboxylic acid with α-haloalkylphenyl sulfide,[4] reaction of dithioacetal[5] with mercuric acetate,[2a] and anodic oxidation of sulfide.[2b,6] However, these methods were always applied to the preparation of α-acetoxyalkyl sulfide **3a**, but not other α-alkanoyloxyalkyl sulfides **3b-d** and α-alkenoyloxyalkyl sulfides **3e-f**.

Enzyme-assisted addition reactions have been studied over the years.[7,8] The use of hydrolytic enzymes as chiral catalyst for asymmetric Michael addition reaction to introduce a center of chirality into fluorocompounds has been described.[7] Kamal[8] *et al.* reported the enzymatic intramolecular cyclizations of ethyl β-2-aminoanilinocrotonates by catalase. Our recent interest in enzyme catalyzed reactions in organic synthesis[9] led us to study the lipase-catalyzed addition reactions of vinyl esters **1** with thiols **2** (Scheme I).

RESULTS AND DISCUSSION

The addition of thiols to vinyl esters were carried out in the presence of a lipase (5 mass equivalents). Several factors were studied in order to investigate the scope of these reactions.

Scheme I



1 **2** **3**

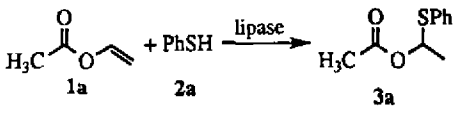
	R	R^1
3a	CH_3-	C_6H_5-
3b	$CH_3(CH_2)_2$-	C_6H_5-
3c	$(CH_3)_2CH$-	C_6H_5-
3d	$CH_3(CH_2)_3$-	C_6H_5-
3e		C_6H_5-
3f		C_6H_5-
3g	CH_3-	CH_3OCOCH_2-
3h	CH_3-	$C_6H_5CH_2$-
3i	CH_3-	*p*-$NO_2C_6H_4$-
3j	CH_3-	*p*-$MeOC_6H_4$-

Influence of the Enzyme

In Table 1, it shows the results of the addition reactions of vinyl acetate **1a** with thiophenol **2a** catalyzed by lipases (5 mass equivalents). Three kinds of commercially available lipases were used. They are porcine pancreatic lipase (PPL), *Candida cylindracea* lipase (CCL) and Pseudomonas lipase (PSL).

While we found that the PSL could catalyze the addition reactions in benzene at 40 °C for three days to give product **3a** in 38% yield (entry b), increasing the reaction temperature to 60 °C, improve the yield to 73% (entry c). The PPL didn't catalyze the addition reaction. Instead a 83% yield of diphenyl disulfide was obtained (entry d). The CCL was also not effective, it gave only 5% yield (entry e).

Table 1. Lipases Catalyzed the Addition Reactions of Vinyl Acetate with Thiophenol



entry	catalyst[a]	solvent	temperature (°C)	reaction time (day)	yield (%)
a	–	toluene	120	7	0
b	PSL	benzene	40	3	38
c	PSL	toluene	60	3	73
d	PPL	hexane	40	3	0[b]
e	CCL	CCl_4	40	7	5
f	H_2SO_4[c]	toluene	80	1	0[d]

[a] PSL: Pseudomonas Lipase; PPL: Porcine Pancreatic Lipase; CCL: *Candida Cylindracea* Lipase; 5 mass equivalents of enzyme were used.
[b] 83% diphenyldisulfide was obtained.
[c] Catalytic amount conc. H_2SO_4 was used.
[d] 100% diphenylthioacetal was obtained.

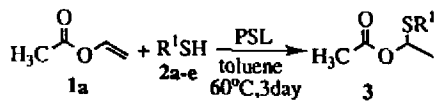
The PSL is essential, because in its absence the addition reaction didn't occur even though the reaction temperature was increased to 120 °C and we recovered most of the starting material (entry a). Under acidic condition, the diphenylthioacetal was obtained in quantitative yield (entry f).

Under the lipase catalyzed condition, the difference between the reaction of vinyl acetate with thiophenol and with alcohol maybe due to the acidity of thiophenol in comparison with alcohol. So, the thiophenol could proceed the addition reaction to vinyl double bond.

Influence of the Nucleophile

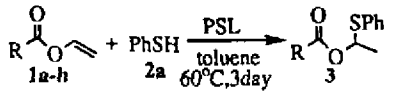
Next, we examined the effect of the nucleophile to the addition reactions. Under the optimized condition, the addition reactions of several other thiols **2a-e** to the vinyl acetate **1a** were performed (Table 2).

Table 2. The Addition Reactions Vinyl Acetate with Several Thiols Catalyzed by PSL



entry	R	product (yield/%)
a	C_6H_5-	**3a** (73)
b	*p*-$CH_3OC_6H_4$-	**3j** (40)
c	*p*-$NO_2C_6H_4$-	**3i** (50)
d	$C_6H_5CH_2$-	**3h** (85)
e	CH_3OCOCH_2-	**3g** (50)

Table 3. The Addition Reactions of Several Vinyl Esters with Thiophenol Catalyzed by PSL



entry	R	product (yield/%)
a	CH_3-	**3a** (73)
b	$CH_3(CH_2)_2$-	**3b** (57)
c	$(CH_3)_2CH$-	**3c** (66)
d	$CH_3(CH_2)_3$-	**3d** (55)
e		**3e** (50)
f		**3f** (35)
g	C_6H_5-	**3k** (0)[a]
h	Ph 	**3l** (0)[a]

[a] The hydrolysis products were obtained in 35% and 95% yields, respectively.

Five thiols were tested, including thiophenol **2a**, *p*-methoxybenzenethiol **2b**, *p*-nitrobenzenethiol **2c**, benzylmercaptan **2d** and methyl thioglycolate **2e**. All of them gave satisfactory results (40-85%). Both the thiophenol and the benzylmercaptan furnished the adducts in good yield (entries a,d). It is noteworthy that both the electron donor group (*i.e.* OCH_3) and electron withdrawing group (*i.e.* NO_2) in the aromatic thiols have negative effects in yields (entries b,c).

Influence of the Substrate

In Table 3, it shows the results of the addition reactions of several vinyl esters **1a-h** with thiophenol **1a** catalyzed by PSL in toluene at 60 °C.

According to the results, vinyl esters of aliphatic acids [saturated (entries a-d) or unsaturated (entries e,f)]·gave adducts were obtained in reasonable yields (35-73%). When R was phenyl or 2-phenylethenyl, hydrolysis occurred only (entries g,h).

When isopropenyl acetate reacted with thiophenol, the transesterification product was obtained in 45% yield. No addition product was formed.

CONCLUSIONS

The addition reactions of vinyl esters with thiols in the presence of PSL provides a convienient methods for the preparation of α-arylthioalkyl esters (35-85% yield). These products can be used as bifunctional substrates or radical precursors.

EXPERIMENTAL SECTION

Instrumentation

Elemental analysis was carried out on a Perkin-Elmer 2400C. Infrared spectra were measured on a JASCO IR Report-100 infrared spectrophtometer. ^{1}H-NMR spectra were recorded at 60 MHz (Varian EM 360L spectrometer) or 300 MHz (Bruker AM-300WB spectrometer), tetramethylsilane served as internal standard. Mass spectra were recorded (Finnigan TSQ-46C spectrometer) at an ionizing voltage 20 eV. High-resolution mass spectra (HRMS) were recorded on JEOL JMS-HX 110 spectrometer. Melting points were determined on a Buchi 535 melting point apparatus.

Material

TLC analysis was performed with Merck silica gel sheets (Kieselgel 60 F_{254}). Column chromatography was performed with silica gel 60 (Merck, 70-230 mesh ASTM). Pseudomonas lipase (PSL) was obtained from Amano company. Porcine pancreatic lipase (PPL, Type II, crude) and *Candida Cylindracea* lipase (CCL, Type VII) were commercial available from Sigma company. Published procedures were used for the synthesis of vinyl esters.[10]

General Procedure for the Thiol Addition Reaction

To a solution of the vinyl ester (0.46 mL, 5 mmol) and thiophenol (0.26 mL, 2.5 mmol) in toluene (25 mL) was added PSL (2 g) at room temperature. The mixture was stirred at 60 °C for 3 days. The reaction mixture was filtered and rinsed with ether. The filtrate was concentrated by rotary evaporator. The residue was purified on a silica gel column chromatography by elution with EtOAc/*n*-hexane (1:10) to give product.

1-(Phenylthio)ethyl Acetate 3a

Colorless oil; IR (neat) 3055, 2975, 1740, 1703, 1435, 1365, 1220, 1060 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 7.11-7.38 (5H, m), 6.08 (1H, q, J = 6.4 Hz), 1.87 (3H, s), 1.40 (3H, d, J = 6.4 Hz); MS *m/z* (relative int.) 196 (8, M$^+$), 152 (27), 110 (100); HRMS calcd for $C_{10}H_{12}SO_2$: 196.0553; found: *m/z* 196.0548; Anal. calcd for $C_{10}H_{12}SO_2$: C, 61.20; H, 6.16%; found: C, 60.94; H, 6.04%.

1-(Phenylthio)ethyl Butanoate 3b

Colorless oil; IR (neat) 3050, 2960, 2925, 1736, 1475, 1438, 1165, 1060 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 7.12-7.48 (5H, m), 6.19 (1H, q, J = 6.2 Hz), 2.21 (2H, t, J = 7.0 Hz), 1.30-1.69 (5H, m), 0.92 (3H, t, J = 7.0 Hz); MS *m/z* (relative int.) 224 (5, M$^+$), 180 (25), 71 (100); HRMS calcd for $C_{12}H_{16}SO_2$: 224.0869; found: *m/z* 224.0867.

1-(Phenylthio)ethyl 2-Methylpropionate 3c

Colorless oil; IR (neat) 3052, 2950, 2930, 1730, 1463, 1435, 1053 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 7.11-7.46 (5H, m), 6.15 (1H, q, J = 6.3 Hz), 2.21-2.68 (1H, m), 1.46 (3H, d, J = 6.3 Hz), 1.08 (6H, d, J = 7.0 Hz); MS *m/z* (relative int.) 224 (9, M$^+$), 180 (28), 137 (35), 71 (100); HRMS calcd for $C_{12}H_{16}SO_2$: 224.0869; found: *m/z* 224.0877.

1-(Phenylthio)ethyl Pentanoate 3d

Colorless oil; IR (neat) 3050, 2951, 1735, 1435, 1160, 1058 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 7.12-7.48 (5H, m), 6.19 (1H, q, J = 6.4 Hz), 2.24 (2H, t, J = 7.0 Hz), 1.18-1.62 (7H, m), 0.89 (3H, t, J = 6.0 Hz); MS *m/z* (relative int.) 238 (9, M$^+$), 194 (22), 137 (38), 85 (100); HRMS calcd for $C_{13}H_{18}SO_2$: 238.1032; found: *m/z* 238.1027.

1-(Phenylthio)ethyl 3-Butenoate 3e

Colorless oil; IR (neat) 3080, 2995, 1742, 1480, 1442, 1243, 1164, 1065 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 7.12-7.42 (5H, m), 6.20 (1H, q, J = 6.2 Hz), 5.51-5.82 (1H, m), 5.11-5.25 (1H, m), 4.85-5.04 (1H, m), 3.02 (2H, d, J = 7.0 Hz), 1.52 (3H, d, J = 6.4 Hz); MS *m/z* (relative int.) 222 (6, M$^+$), 179 (100), 137 (27); HRMS calcd for $C_{12}H_{14}SO_2$: 222.0723; found: *m/z* 222.0717.

1-(Phenylthio)ethyl 2(E)-butenoate 3f

Colorless oil; IR (neat) 3050, 2970, 2930, 1709, 1652, 1465, 1435, 1290, 1168, 1058 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 7.11-7.40 (6H, m), 6.21 (1H, q, J = 6.4 Hz), 5.74 (1H, d, J = 16 Hz), 1.84 (3H, dd, J = 7.0, 1.8 Hz), 1.50 (3H, d, J = 6.4 Hz); MS *m/z* (relative int.) 222 (5, M$^+$), 178 (11), 137 (17), 69 (100); HRMS calcd for $C_{12}H_{14}SO_2$: 222.0723; found: *m/z* 222.0731.

Methyl S-(1-acetoxyethyl)thioglycolate 3g

Colorless oil; IR (neat) 2980, 2950, 1740, 1735, 1430, 1370, 1212, 1061 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 6.09 (1H, q, J = 6.4 Hz), 3.69 (3H, s), 3.38 (2H, d, J = 3.2 Hz), 2.10 (3H, s), 1.57 (3H, d, J = 6.4 Hz); MS *m/z* (relative int.) 192 (4, M$^+$), 148 (22), 118 (20), 87 (28), 74 (35), 46 (100); HRMS calcd for $C_7H_{12}SO_4$: 192.0447; found: *m/z* 192.0438.

1-(Benzylthio)ethyl Acetate 3h

Colorless oil; IR (neat) 3051, 3020, 2975, 2925, 1738, 1690, 1452, 1362, 1222, 1058 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.19-7.28 (5H, m), 5.59 (1H, q, J = 6.5 Hz), 3.86 (1H, d, J = 13.5 Hz), 3.77 (1H, d, J = 13.5 Hz), 1.92 (3H, s), 1.47 (3H, d, J = 6.5 Hz); MS *m/z* (relative int.) 166 (8), 150 (42), 91 (100); HRMS calcd for $C_{11}H_{14}SO_2$: 210.0721; found: *m/z* 210.0727.

1-(*p*-Nitrophenylthio)ethyl Acetate 3i

Yellow solid; m.p. 50-52 °C; IR (neat) 3052, 2980, 1740, 1730, 1572, 1508, 1340, 1206, 1060 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 8.08 (2H, d, J = 9.0 Hz), 7.45 (2H, d, J = 9.0 Hz), 6.32 (1H, q, J = 6.4 Hz), 2.04 (3H, s), 1.58 (3H, d, J = 6.4 Hz); MS *m/z* (relative int.) 241 (12, M^+), 197 (18), 182 (20), 87 (100); HRMS calcd for $C_{10}H_{11}NSO_4$: 241.0430; found: *m/z* 241.0438.

1-(*p*-Methoxyphenylthio)ethyl Acetate 3j

Colorless oil; IR (neat) 2950, 2870, 1738, 1585, 1490, 1241, 1223 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 60 MHz) δ 7.43 (2H, d, J = 9.0 Hz), 6.82 (2H, d, J = 9.0 Hz), 6.09 (1H, q, J = 6.1 Hz), 3.75 (3H, s), 2.02 (3H, s), 1.45 (3H, d, J = 6.1 Hz); MS *m/z* (relative int.) 226 (28, M^+), 182 (29), 140 (100).

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Key Words

Addition; Lipase; Vinyl esters; Thiols.

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