A New Methodology for the Preparation of Vinyl Esters

Michael I. Weinhouse, Kim D. Janda*

Departments of Molecular Biology and Chemistry, The Scripps Research Institute, 10666 N. Torrey Pines Road, La Jolla, California 92037, USA

Received 24 March 1992; revised 3 June 1992

A new methodology has been developed for the preparation of unsubstituted enol esters. Its application is demonstrated by the obtainment of vinyl aromatic α-amino esters. A brief investigation of the preparation of other hydrophobic vinyl esters proved successful. Because of the mild reaction conditions employed, it is believed this route should provide access to other enol esters.

The immense potential of enzymes as catalysts in organic synthesis is well documented.[1] One group of enzymes which has drawn much attention are lipases.[2] These hydrolases can catalyze not only their "natural" reaction of hydrolysis but also that of transesterification.[3] A convenient way to make these enzymatic transesterifications essentially irreversible is to employ enol esters as the acylating agent.[1,3] Recently, we have identified specific monoclonal antibodies which mimic lipases in their catalytic mode of action.[4-6] To further investigate the properties of these, and other catalytic antibodies, required the synthesis of phenylalanine derived unsubstituted enol esters. The need for such unsubstituted enol esters stemmed from steric constraints imposed by the anitbody binding pocket. Herein we report a convenient methodology for obtaining these and other vinyl esters.

Three major methods exist for the synthesis of enol carboxylates: (1) Treatment of aldehydes or ketones under acidic or basic conditions with the appropriate acid anhydride or chloride.[7,8] (2) The acetoxylation of olefins promoted by palladium acetate.[9,10] (3) The addition reaction of carboxylic acids to alkynes in which mercury salts[11] or ruthenium complexes are used as catalysts.[12,13] While these methods are useful, they can be deleterious to molecules (in our case protected amino acids) which are susceptible to decomposition via acid/base or high temperature. Furthermore, the latter two procedures described above can give rise to unwanted regioisomers.

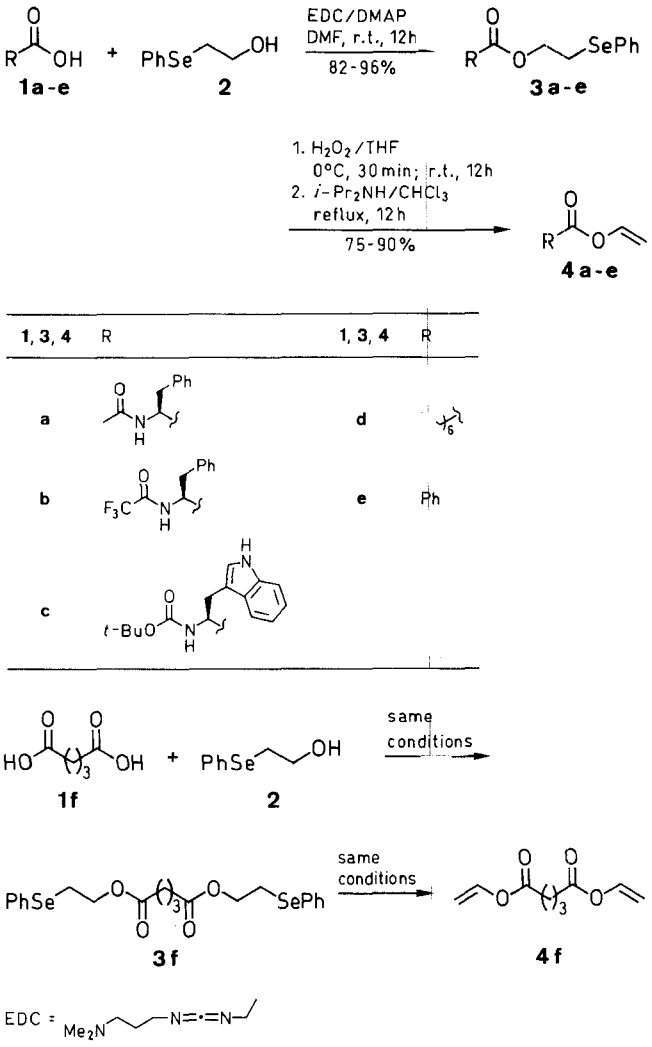
The development in recent years of a large number of selenium-based synthetic methods has made significant contributions to synthetic organic chemistry. Of special value is organoselenium-mediated olefinations, however, such eliminations have yet to be applied for the prepara-

tion of enol esters.[14] The scheme describes below our selenium based methodology used to obtain unsubstituted vinyl esters.

Our goal being *N*-protected phenylalanine vinyl esters; thus esterification of 2-(phenylseleno)ethanol[15] **(2)**, with *N*-acetyl or *N*-(trifluoroacetyl)phenylalanine provided **3a** or **3b**, (Table 1). The oxidation of these selenides is accomplished using an excess of hydrogen peroxide (30%). While the selenoxides could be isolated, it is much more advantageous to remove the remaining peroxide via extraction and reflux the crude mixture in chloroform. Flash chromatography provides the chemically pure vinyl esters **4a** and **4b**. Their optical purity can be demonstrated by hydrolysis of the ester functionality, under mild conditions (pH 9.0, 100 mM Aces 0.52 mM tris, 0.52 mM ethanolamine, r.t., $t_{1/2} = \sim 50$ min); this then restoring optically pure starting materials **1a** and **1b**, respectively.

A brief exploration of the utility of our methodology led us to look at Boc-tryptophan. Its vinyl ester was produced in almost 81% yield from selenide **3c**. Two additional hydrophobic molecules, octanoic acid **(1d)** and benzoic acid **(1e)** were investigated, these also gave respectable yields of vinyl esters **4d** and **4e**, (Table 2). Finally, we looked at glutaric acid **(1f)**, the disubstituted enol ester **4f** was also obtained in a reasonable yield, (Table 2).

In conclusion, an expedient route to unsubstituted vinyl esters has been developed. We have applied this methodology to obtain vinyl α-amino esters. A brief investigation of other hydrophobic acids was accomplished with good success. The methodology devised should be amendable to other α-amino/carboxylic acids due to the simple protocol and mild reaction conditions utilized. An application of such vinyl ester subtrates in enzyme and abzyme catalysis appears promising.[1]



Reactions were carried out in flame-dried glassware under an atmosphere of N_2. Reagent and solvent transfers were made with oven-dried syringes and needles. $CHCl_3$ was continuously distilled from CaH_2. Tetrahydrofuran (THF) was distilled from Na/benzophenone ketyl. All reagents were purchased from Aldrich Chemical Company. All chromatography solvents were monitored by analytical thin-layer chromatographic methods (TLC) with the use of E. Merck silica gel 60 F glass plates (0.25 mm). Flash chromatography was carried out with the use of E. Merck silica gel 60 (230–400 mesh) as described by Still.[16] Compound **2** was synthesized as previously described.[15] Microanalyses (C,H,N) were performed by Galbraith Laboratories, Knoxville, Tennessee.

Caution. Selenium compounds are toxic and should be handled with due care.

Table 1. Selenides **3a–f** Prepared

Starting Acid	Product	Yield (%)	mp (°C)[a]	Molecular Formula[b]	^1H NMR ($CDCl_3$/TMS)[c] δ, *J* (Hz)
1a	**3a**	92	oil	$C_{19}H_{21}NO_3Se$ (390.3)	7.5 (m, 2H), 7.25 (m, 5H), 7.1 (m, 3H), 5.95 (d, 1H, *J* = 9.4), 4.8 (m, 1H), 4.30 (m, 2H), 3.1 (m, 4H), 1.95 (s, 3H)
1b	**3b**	88	oil	$C_{19}H_{18}F_3NO_3Se$ (444.3)	7.6–7.5 (m, 2H), 7.35–7.2 (5H), 7.1–7.0 (m, 3H), 6.8 (d, 1H, *J* = 11.0), 4.85–4.7 (m, 1H), 4.45–4.2 (m, 2H), 3.2–3.0 (m, 4H)
1c	**3c**	85	93–94	$C_{24}H_{28}N_2O_4Se$ (487.4)	8.2 (br s, 1H), 7.55–7.4 (m, 3H), 7.3–6.9 (m, 7H), 5.10 (d, 1H, *J* = 7.0), 4.55 (m, 1H), 4.2 (m, 2H), 3.2 (m, 2H), 2.90 (t, 2H, *J* = 5.0), 1.4 (s, 9H)
1d	**3d**	96	oil	$C_{16}H_{24}O_2Se$ (415.2)	7.5 (m, 2H), 7.2 (m, 3H), 4.3 (t, 2H, *J* = 6.0), 3.1 (t, 2H, *J* = 6.0), 2.25 (t, *J* = 8.0, 2H), 1.7–1.5 (m, 2H), 1.3–1.1 (m, 8H), 0.85 (t, 3H, *J* = 8.0)
1e	**3e**	91	oil	$C_{15}H_{14}O_2Se$ (305.2)	7.95 (d, 1H, *J* = 9.0), 7.6–7.5 (m, 3H), 7.45–7.35 (m, 2H), 7.3–7.2 (m, 3H), 4.55 (t, 2H, *J* = 9.0), 3.2 (t, 2H, *J* = 9.0)
1f	**3f**	82	oil	$C_{21}H_{24}O_4Se_2$ (498.3)	7.55 (m, 4H), 7.2 (m, 6H), 4.3 (t, 4H, *J* = 7.0), 3.05 (t, 4H, *J* = 7.0), 2.3 (t, 4H, *J* = 9.0), 1.9–1.8 (m, 2H)

[a] Uncorrected, measured with a Fisher-Johns melting point apparatus.
[b] Satisfactory microanalyses obtained C ± 0.40, H ± 0.34, N ± 0.40.
[c] Recorded on a Bruker AM-360 spectrometer.

Table 2. Vinyl Esters **4a–f** Prepared

Starting Selenide	Product	Yield (%)	mp (°C)[a]	Molecular Formula[b]	^{1}H NMR ($CDCl_3$/TMS)[c] δ, J (Hz)
3a	**4a**	90	56–58	$C_{13}H_{15}NO_3$ (233.3)	7.3–7.1 (m, 6H), 6.4 (d, 1H, J = 9.0), 5.0–4.9 (m, 2H), 4.65 (m, 1H), 3.25–3.05 (m, 2H), 1.95 (S, 3H)
3b	**4b**	77	oil	$C_{13}H_{12}F_3NO_3$ (287.2)	7.5–7.4 (m, 2H), 7.3–7.2 (m, 4H), 7.1 (d, 1H, J = 9.0), 5.1–4.9 (m, 2H), 3.3–3.2 (m, 2H)
3c	**4c**	81	125–127	$C_{18}H_{22}N_2O_4$ (330.4)	8.25 (br s, 1H), 7.5 (d, 1H, J = 9.0), 7.3 (d, 1H, J = 9.0), 7.2–7.05 (m, 3H), 6.9 (br s, 1H), 5.1 (d, 1H, J = 9.0), 4.95 (d, 1H, J = 18.0), 4.7 (m, 1H), 4.6 (d, 1H, J = 9.0), 3.3 (m, 2H), 1.4 (s, 9H)
3d	**4d**	84	oil	$C_{10}H_{18}O_2$ (170.3)	7.3–7.2 (m, 1H), 4.85 (d, 1H, J = 16.0), 4.55 (m, 1H, J = 8.0), 2.35 (t, 2H, J = 9.0), 1.7–1.55 (m, 2H), 1.35–1.2 (m, 8H), 0.9 (t, 3H, J = 9.0)
3e	**4e**	82	oil	$C_9H_8O_2$ (148.1)	8.1 (d, 2H, J = 5.0), 7.6–7.4 (m, 4H), 5.1–5 (d, 1H, J = 15.0), 4.7 (d, 1H, J = 4.0)
3f	**4f**	75	oil	$C_9H_{12}O_4$ (184.2)	7.3–7.2 (m, 2H), 4.9 (d, 2H, J = 16.0), 4.6 (d, 2H, J = 5.0), 2.45 (t, 4H, J = 9.0), 2.1–2.0 (m, 2H)

[a] Uncorrected, measured with a Fisher-Johns melting point apparatus.
[b] Satisfactory microanalyses obtained C ± 0.35, H ± 0.30, N ± 0.38.
[c] Recorded on a Bruker AM-300 spectrometer.

2-(Phenylseleno)vinyl Esters 3; General Procedure:
To a stirring of 2-(phenylseleno)ethanol (**2**; 800 mg, 4.0 mmol) in DMF (9 mL) was added 4-dimethylaminopyridine (DMAP, 980 mg, 0.8 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 1.15 g, 6 mmol) and the acid (5.2 mmol). The reaction was allowed to stir at r.t. for 12 h. The mixture was diluted with EtOAc (50 mL), followed by the cautious addition of aq HCl (0.5 M, 25 mL). The layers were separated, and the organic layer was extracted again with HCl (0.5 M, 25 mL). The phases were separated again and the organic layer was washed with brine (2 × 25 mL), dried (Na_2SO_4), filtered, and stripped. The crude product was flash chromatographed affording the pure selenide esters **3**.

Vinyl Esters 4; General Procedure:
A stirred solution of **3** (5 mmol) in THF (25 mL) was cooled to 0 °C. H_2O_2 30% (10 equiv) was added dropwise over a 5 min period. After stirring at 0 °C for 30 min the ice bath was removed and the solution was stirred for 12 h at r.t. The mixture was diluted with $CHCl_3$ (75 mL), washed with H_2O (3 × 50 mL), brine (2 × 50 mL), dried (Na_2SO_4), filtered and stripped. The crude selenoxide was dissolved in $CHCl_3$ to make a 0.02 M solution and this was refluxed for 12 h. In cases **3d–f** *i*-Pr_2NH (10 mmol, 2 equiv) was added. The mixture was evaporated and the crude product was flash chromatographed affording pure vinyl esters **4**.

This work was assisted financially by generous grants from the National Institute of Health, the National Science Foundation and The Scripps Research Institute.

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