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Synthesis of Higher α-Chlorovinyl and α-Bromovinyl Amino Acids: The Amino Protecting Group Determines the Reaction Course

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Abstract

N-Trifluoroacetyl α-vinyl amino esters are smoothly converted to the corresponding α-chlorovinyl or α-bromovinyl amino esters through the agency of phenyselenyl chloride or phenylselenyl bromide, respectively, followed by oxidation and pyrolysis. Exclusively the (E)-extemal halovinyl isomer and the internal halovinyl isomer are observed. The amino protecting group is a critical determinant of the reaction course (alkene addition vs. 5-exo-trig-like cyclization).

As part of a program directed at the synthesis of α-branched amino acids[1] as potential inhibitors of pyridoxal-dependent enzymes, and as building blocks for unnatural peptide synthesis, we sought a synthetic route to α-halovinyl amino acids. Early on, Abeles had postulated that halovinyl amino acids might serve as “Trojan horse” inhibitors for amino acid-processing enzymes via PLP-catalyzed elimination of the elements of hydrogen halide to yield a reactive allenic intermediate.[2] In fact, 3-chlorovinylglycine has been shown to produce efficient mechanism-based inhibition of alanine racemase.[3] 3-Fluorovinylglycine irreversibly inhibits both alanine racemase[3] and tryptophan synthase.[4] Additionally, the internal γ- and external γ-(E)- and γ-(Z)-fluotovinyl-GABA analogs inactivate GABA transaminase by related mechanisms.[5]

It follows that the higher halovinyl amino acids[6] could in principle produce analogous enzyme-bound alleneimine intermediates through enzyme-catalyzed decarboxylative halide elimination in amino acid decarboxylase active sites. However, a synthetic route to higher halovinyl amino acids had not yet been described.[7] We had developed a reliable and quite general method by which α-vinyl amino acids could be accessed by formal α-vinylation of the protected α-amino acids (Scheme 1).[1c,d,8] We envisioned that α-vinyl amino acids, in turn, could be employed as direct precursors to α-chlorovinyl and α-bromovinyl amino acids.

Raucher had described a two step procedure wherein addition of phenylselenyl bromide (chloride) to an alkene, followed by selenide oxidation and pyrolysis, produces the corresponding halovinyl olefin.[9,10] Indeed, this procedure was employed by Thomberry et al. for the synthesis of 3-chlorovinylglycine.[3a] However, in that case, beginning from N-Cbz-vinylglycine methyl ester, this two step sequence afforded N-Cbz-3-chlorovinylglycine methyl ester in a modest 15–20% yield. We set out to examine this reaction closely in the context of more sterically encumbered α-vinyl amino acids. Since our α-vinylation procedure yields α-vinyl amino acids protected as the N-benzoyl methyl esters directly, we

initially examined the compatibility of this protecting group scheme with the Raucher chemistry.

In fact, for the vinylphenylalanine derivative **1**, treatment with PhSeCl or PhSeBr in MeCN at 0→25°C reproducibly yields oxazoline **2** in nearly quantitative yield, following ozone-mediated oxidation and pyrolysis (Scheme 2).[11] Thus, in this system, intramolecular 5-exo-trig-like cyclization of the benzamido carbonyl upon the episelenonium ion intermediate apparently out-competes intermolecular trapping with chloride ion. This cyclization is likely facilitated by the gem-dialkyl effect in these α-branched amino acid derivatives. As an alternative to N-benzoyl protection, the N-Cbz, benzyl ester protecting group motif is readily accessible for higher α-vinyl amino acids.[12] Hence, we subjected the so-protected vinylphenylalanine derivative **3** to the Raucher conditions (PhSeCl in MeCN at 0→25°C). Here too, a facile 5-exo-trig-like cyclization is observed, with the carbamato carbonyl serving as the internal nucleophile and with concomitant debenzylation. Appreciable quantities of oxazolidinone **4** (54% yield, Scheme 2) are isolated after oxidation and pyrolysis.[13] It is conceivable that an analogous side reaction accounts for the low yield in the reported addition of phenylselenyl chloride to N-Cbz-protected vinylglycine.[3a]

Therefore, it became clear that an α-amino protecting group with reduced nucleophilicity would be necessary. We chose the N-trifluoroacetyl group. Gratifyingly, with this protecting group, the 5-exo-trig-like cyclization manifold is effectively suppressed, so that efficient addition of PhSeX across the alkene is observed (Table 1). For short reaction times, predominantly anti-Markovnikov orientation is observed, leading to the (E)-extemal chlorovinyl product (**6**). Long reaction times in CH_3CN or CH_2Cl_2 (but not DMF or CCl_4) lead to a nearly equal mixture of internal (**7**) and external chlorovinyl products (**6**) for all side chains examined. Of the solvents examined, only AcOH leads exclusively to the internal chlorovinyl product **7**, albeit in low yield.

The same strategy could be employed for the synthesis of protected bromovinyl amino acids by substituting PhSeBr for PhSeCl (Table 2). However, PhSeBr showed a greater propensity to add in a Markovnikov fashion, even with short reaction times, yielding a mixture of internal (**9**), and (E)-external bromovinyl (**8**) isomers. A typical procedure for the two-step sequence is as follows: To a solution of methyl N-trifluoroacetyl-α-vinylphenylalaninate (110 mg, 0.37 mmol) in freshly distilled CH_3CN (0.9 mL) is added PhSeCl (70 mg, 0.37 mmol) in CH_3CN (0.9 mL) at 0°C. The reaction mixture is allowed to warm to rt and stirred for 12 h. Following evaporation of the solvent, the crude selenide is taken up in CH_2Cl_2 (15 mL) and cooled to −78°C. Through this solution is bubbled O_3 until a blue color persists. Following an Ar purge, this solution of selenoxide(s) is transferred dropwise into refluxing PhH (40 mL) and heating is continued an additional 30 min. Evaporation of the volatiles and SiO_2 chromatography (40% EtOAc-hexanes) yields **6** (R = CH_2Ph; 106 mg, 87%).

In summary, provided that an electron-poor N_α-protecting group (e.g. trifluoroacetyl) is employed, α-vinyl amino acids, themselves readily available from the parent amino acids,[1c,d,8] are smoothly parlayed into the corresponding α-halovinyl (X = Cl, Br) amino acids by the sequence: (i) PhSeX, rt; (ii) O_3, −78°C; (iii) PhH, reflux. The ratio of

Markovnikov (internal halovinyl) to anti-Markovnikov [(E)-extemal halovinyl] product is largely a function of reaction time, with longer times favoring the former isomer.

Acknowledgments

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6. We define higher α-halovinyl amino acids as α-amino acids bearing the usual α-side chain (≠H) and an additional halovinyl substituent in place of the usual α-proton.
7. To our knowledge, there is only one previously reported synthesis of a higher α-halovinyl amino acid. Namely, treatment of 3,4-dimethoxy-α-ethynylphenylalanine with 47% HBr at reflux for 4 h yields internal α-bromovinyl-DOPA in 31% yield: reference[8j].
8. For other synthetic approaches to higher α-vinyl amino acids, see:(a) Colson P-J, Hegedus LS. J Org Chem. 1993; 58:5918–5924.(b) Seebach D, Bürger HM, Schickli CP. Liebigs Ann Chim. 1991:669–684.(c) Castelhano AL, Horne S, Taylor GJ, Billedeau R, Krantz A. Tetrahedron. 1988; 44:5451–5466.(d) Münster P, Steglich W. Synthesis. 1987:223–225.(e) Castelhano AL, Home S, Billedeau R, Krantz A. Tetrahedron Lett. 1986; 27:2435–2438.(f) Weber T, Aeschimann R, Maetzke T, Seebach D. Helv Chim Acta. 1986; 69:1365–1377.(g) Steglich W, Wegmann H. Synthesis. 1980:481–483.(h) Metcalf BW, Bonilavri E. J Chem Soc Chem Commun. 1978:914–915.(i) Greenlee WJ, Taub D, Patchett AA. Tetrahedron Lett. 1978:3999–4002.(j) Metcalf BW, Jund K. Ibid. 1977:3689–3692.(k) Taub D, Patchett AA. Ibid. 1977:2745–2748.
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11. For 2: ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.25 (d, *J* = 14 Hz, 1 H), 3.50 (d, 7=14 Hz, 1 H), 3.78 (s, 3 H) ; 4.72 (d, *J* = 3.2 Hz, 1 H), 4.97 (d, *J* = 3.2 Hz, 1 H), 7.16–7.20 (m, 3 H), 7.23–7.25 (m, 2 H), 7.39–7.42 (m, 2 H), 7.49–7.51 (m, 1 H); 7.92–7.94 (m, 2 H); MS (methane-CI) *m/z* (rel int): 307 (M^+, 1), 248 (− CO_2Me, 7), 216 (− Bn, 100), 105 (48), 91 (47), 77 (56); HRMS (FAB, 3-NOBA) calcd for $C_{19}H_{18}NO_3$ $(M+H)^+$ 308.1287, obsd 308.1278.
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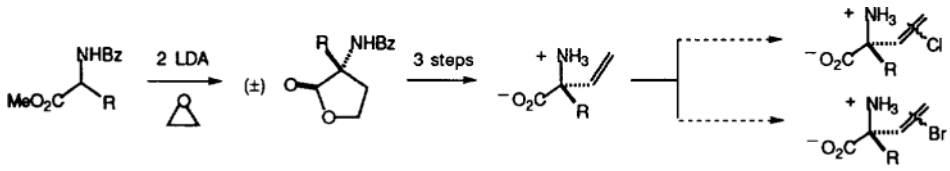
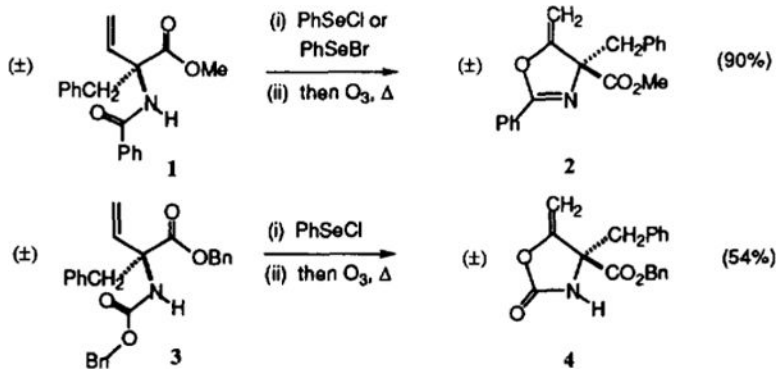
13. For 4: ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.06 (d, *J* = 13.5 Hz, 1 H), 3.46 (d, *J* = 13.5 Hz, 1 H), 4.79 (d, *J* = 3.4 Hz, 1 H), 4.91 (d, *J* = 3.4 Hz, 1 H), 5.14 (d, *J* = 11.5 Hz, 1 H), 5.18 (d, *J* = 11.5 Hz, 1 H), 5.39 (br s, 1 H), 7.05 (m, 2 H), 7.21-7.25 (m, 6 H), 7.35–7.37 (m, 2 H); MS (methane-CI) *m/z*

(rel int): 324 (M+H, 1), 281 (1), 190 (4), 91 (100); HRMS (FAB, 3-NOBA) calcd for $C_{19}H_{18}NO_4$ $(M+H)^+$ 324.1236, obsd 324.1239.

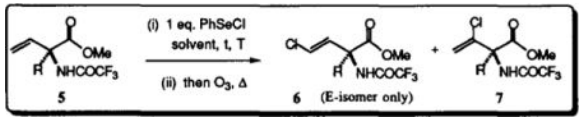


Scheme 1.



Scheme 2.

Table 1



R	Time (hours)	Final Temp. (°C)	Solvent	Yield	External: Internal
Me	2	25	CH_3CN	82%	all external
Me	48	25	CH_3CN	80%	1 : 1
CH_2Ph	12	25	CH_3CN	87%	all external
CH_2Ph	2	40	CH_3CN	71%	all external
CH_2Ph	10	40	CH_3CN	70%	1.3 : 1
CH_2Ph	125	25	CH_3CN	68%	1 : 1
CH_2Ph	115	25	DMF	80%	all external
CH_2Ph	115	25	CCl_4	75%	5 : 1
CH_2Ph	115	25	CH_2Cl_2	95%	1 : 1
CH_2Ar	1.5	25	CH_3CN	79%	all external
CH_2Ar	120	25	CH_3CN	71%	1 : 1
CH_2Ar	120	25	AcOH	25%	all internal
$CHMe_2$	2	25	CH_3CN	64%	all external

Ar = *m*-(*tert*-butyldimethyl)silyloxyphenyl

Table 2

R	Time	Final Temp. (°C)	Solvent	Yield	External: Internal
Me	30 min	0	CCl_4	70%	1 : 2.4
Me	45 min	25	CH_3CN	75%	1 : 1
Me	2 days	25	CH_3CN	67%	1 : 4.3
CH_2Ph	2 h	25	CH_3CN	52%	1 : 1
CH_2Ph	19 h	50	CH_3CN	67%	1 : 6