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Synthesis of Protected Racemic β,γ-Unsaturated-α-Amino Acids via γ-Phenylseleno-α,β-Unsaturated Esters

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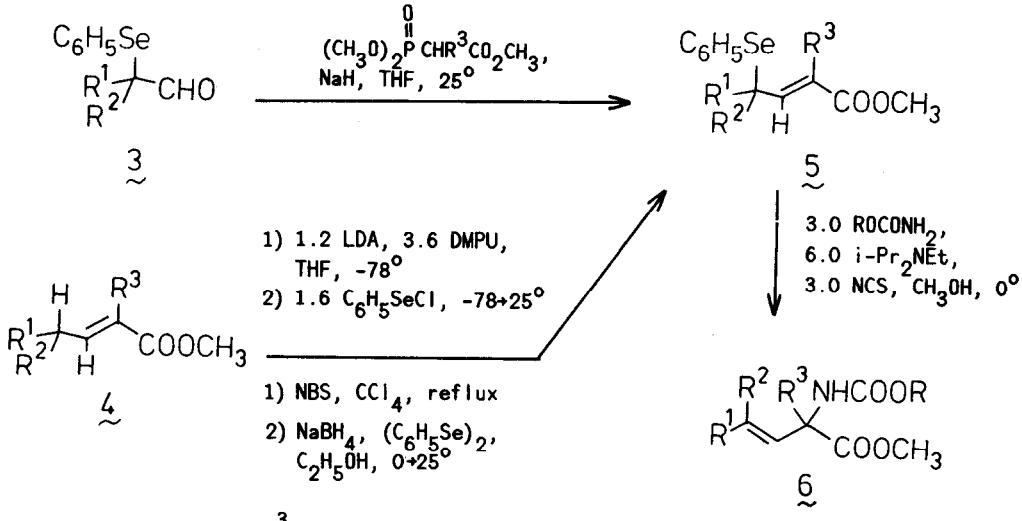
Summary: Oxidative rearrangement of γ-phenylseleno-α,β-unsaturated esters (1) with the N-chlorosuccinimide/N,N-diisopropylethylamine/alkyl carbamate reagent combination affords preparatively useful yields of protected β,γ-unsaturated-α-amino acids (2).

The β,γ-unsaturated-α-amino acids are a class of compounds of considerable biological interest, possessing antibiotic and enzyme inhibitory activity.[2] The chemical sensitivity of these substances has challenged numerous synthetic chemists over the past decade and several successful synthetic routes to this interesting structural class have evolved.[3] We have recently reported a mild regio- and stereocontrolled method for the conversion of allylic selenides to rearranged protected allylic amines.[4] We now report that this process affords a convenient and flexible preparative synthetic entry to racemic protected β,γ-unsaturated-α-amino acids (1→2), which is conceptually distinct from previously reported approaches. This application highlights the efficiency and mildness of the selenide to amine rearrangement.

1 2

Several methods for the preparation of variously substituted γ-phenylseleno-α,β-unsaturated esters, 5, have been explored. As illustrated below and in the accompanying table, Wadsworth-Horner-Emmons homologation of α-phenylselenoaldehydes[5], 3, and selenenylation of γ-extended enolates of α,β-unsaturated esters[6], 4, both represent one-step routes to these substances.[7] More commonly, we have employed a preparatively simple two-step sequence involving allylic bromination with N-bromosuccinimide, followed by displacement of bromide with phenyl selenide anion.

Rearrangement of the allylic selenides to allylic amines (5→6) was effected as previously described.[4,8] In this instance, the use of the hindered base N,N-diisopropylethylamine was preferable to triethylamine, since the resulting α-N-carbamate-protected-β,γ-unsaturated esters (6, R^3=H) are sensitive to base catalyzed rearrangement to the corresponding α,β-unsaturated isomers. One limitation has emerged from this survey: γ,γ-disubstituted selenides (table, entries 5, 6) provide a low yield of the desired rearrangement product.[9]

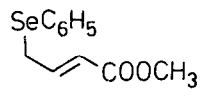
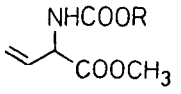
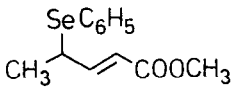
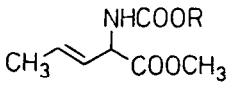
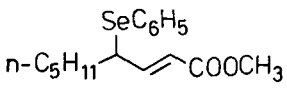
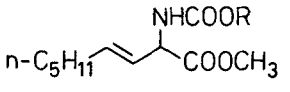
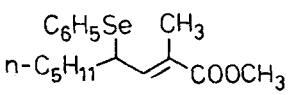
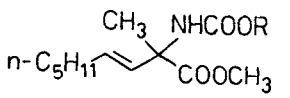
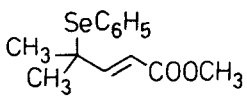
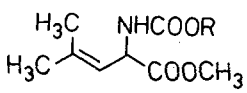
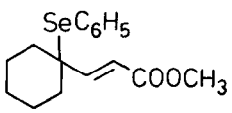
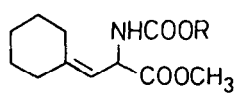
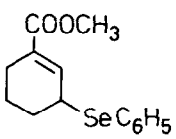
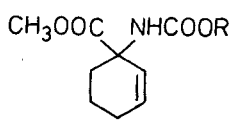


As described elsewhere,[3] the parent β,γ-unsaturated-α-amino acids may be prepared by acid hydrolysis. For example, hydrolysis (6N HCl(aq), 1h, reflux) of 6 (R=t-C_4H_9; R^1=R^2=R^3=H) prepared via the organoselenium route, followed by ion exchange chromatography (Bio-Rad AG 1-X8, 50-100 mesh, OH^- form, 1M aqueous HOAc) and recrystallization from aqueous ethanol afforded (±)-vinylglycine, 48%, m.p. 218-220° dec. (lit.[3c] 218-220° dec.).

The method described herein accommodates a variety of substitution patterns in the starting selenide as well as a variety of carbamate protecting groups and is expected to afford considerable flexibility in the selection of deprotection techniques. A representative experimental procedure follows.

Methyl 2-[[(2,2,2-trichloroethoxy)carbonyl]-amino]-(E)-3-pentenoate. A solution of 200 mg (0.743 mmol) of methyl 4-phenylselenenyl-(E)-2-pentenoate, 429 mg (2.23 mmol) of 2,2,2-trichloroethyl carbamate,[10] 466 mg (4.39 mmol) of trimethyl orthoformate,[8] and *ca.* 2 mg of p-toluenesulfonic acid hydrate in 2.0 ml of methanol at 25° was stirred 30 min., treated with 576 mg (4.46 mmol) of N,N-diisopropylethylamine, and cooled to 0°C. N-Chlorosuccinimide (298 mg, 2.23 mmol) was added and the cold mixture was stirred 10 min. The reaction mixture was acidified to pH 1 with 5% aqueous hydrochloric acid, and was extracted with several portions of ether. The combined ether extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Chromatography on silica gel (eluant: 40% ether/pentane) provided after concentration *in vacuo*, 164 mg (72%) of methyl 2-[[(2,2,2-trichloroethoxy)carbonyl]-amino]-(E)-3-pentenoate as a colorless oil: ^{1}H NMR($CDCl_3$, 500 MHz): δ 5.84(1H, dq, J=15, 7 Hz, CH_3CH=); 5.64 (1H, d, J=6 Hz, NH); 5.50 (1H, dd, J=15, 5Hz, =CHCH:); 4.84 (1H, dd, J=6, 5 Hz, =CHCH:); 4.76 (1H, d, J=13 Hz, $-OCH_aH_bCCl_3$); 4.71 (1H, d, J=13 Hz, $-OCH_aH_bCCl_3$); 3.78 (3H, s, $-OCH_3$); 1.73 (3H, d, J=7 Hz, CH_3CH=); IR: (neat, NaCl) 3440, 3360 (NH), 1750, 1530 (NHC=O), 980 (C=C, trans) cm^{-1}; MS (m/e, EI) 303, 305, 307 (M^+), 244, 246, 248 ($M^+-CO_2CH_3$) 131, 133, 135 ($CCl_3CH_2^+$).[11]

Table. Protected β,γ-unsaturated-α-Amino Acids via γ-Phenylseleno-α,β-Unsaturated Esters

Entry	Selenide[a]	Yield[b] (%)	Protected Amino Acid[a]	Yield[c] (%)
1		63 (C)		62 (R = $-CH_2C_6H_5$) 66 (R = $-t-C_4H_9$)
2		80 (C)		80 (R = $-t-C_4H_9$) 72 (R = $-CH_2CCl_3$)
3		66 (A) 40 (B) 64 (C)		87 (R = $-CH_2C_6H_5$) 61 (R = $-t-C_4H_9$) 77 (R = $-CH_2CCl_3$)
4		66 (A) 51 (C)		73 (R = $-CH_2C_6H_5$) 74 (R = $-CH_2CCl_3$)
5		69 (A)		32 (R = $-t-C_4H_9$)
6		64 (A)		12 (R = $-t-C_4H_9$)
7		58 (B)[d]		30 (R = $-CH_2CCl_3$)

[a] Endnote 7. Alkene stereochemistry assigned by ^1H NMR coupling constants.

[b] A: Wadsworth-Horner-Emmons homologation.
B: Direct selenenylation.
C: Halogenation; Displacement.

[c] Reflects isolated yield of chromatographed product.

[d] Contaminated with *ca.* 20% of a substance believed to be the corresponding α-phenylseleno-β,γ-unsaturated isomer.

References and Endnotes

1. (a) Searle Scholar (1984-1987); (b) Recipient of a Procter & Gamble Exploratory Research Grant (1983-1986).

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7. The selenides, protected β,γ-unsaturated-α-amino acids, and β,γ-unsaturated-α-amino acids described herein were characterized by ^{1}H NMR, IR, and low resolution MS. Selected selenides, protected β,γ-unsaturated-α-amino acids and β,γ-unsaturated-α-amino acids gave correct elemental composition data (exact mass or combustion analysis).

8. The trimethyl orthoformate/acid treatment described in the representative experimental procedure apparently scavenges traces of water from the methanol, selenide, and carbamate and affords a ca. 20% increase in the yield of the rearrangement step.

9. The mechanistic implications of this observation are under investigation and will be discussed in an upcoming full paper.

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