

Se-(9-Fluorenylmethyl) Selenoesters; Preparation, Reactivity, and Use as Convenient Synthons for Selenoacids

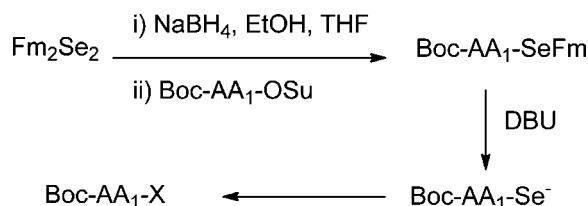
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ABSTRACT



Se-(9-Fluorenylmethyl) selenoesters are readily prepared, stable precursors to selenocarboxylates, which they liberate on treatment with DBU. Fm selenoesters are compatible with the use of TFA for the removal of Boc groups and with simple peptide bond forming reactions. Amino acid derived selenocarboxylates condense directly with amines to give amides, react smoothly with isocyanates and isothiocyanates to give amides, and couple with electron-deficient azides also to give amides.

In recent years, thioacids¹ have featured prominently in the search² for improved methods for amide bond

formation because of (i) their increased acidity with respect to the corresponding carboxylic acids; (ii) the greater nucleophilicity of the thiocarboxylate with respect to the carboxylate anion; and (iii) the increased reactivity of derived thioesters over simple esters toward amines. Amide bond forming reactions based on the thioacid function include (i) reaction with azides and in particular electron-deficient azides;³ (ii) reaction with 2,4-dinitrobenzenesulfonamides and with other electron-deficient arenes in the presence of amines;⁴ (iii) reaction with isocyanates, isothiocyanates, and thiocarbamates;⁵ (iv) reaction with isonitriles;⁶ and (v) direct reaction with amines in the

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presence of silver or copper salts, or other electrophiles.⁷ Selenoacids,⁸ with the more polarizable and more nucleophilic selenium atom,⁹ have the potential for even greater reactivity in amide bond forming reactions, either as direct precursors to amides or as precursors to reactive selenoesters. Indeed, this potential has been recognized by several groups, particularly with respect to the increased reactivity of selenocarboxylates toward simple azides,¹⁰ and has begun to be exploited in the native chemical ligation of peptides.¹¹ The potential of selenoacid chemistry is, however, limited by the instability of selenocarboxylates toward aerobic oxidation and by the limited range of methods developed to generate them in situ. Thus, selenocarboxylates are typically generated by the reaction of metal (hydrogen) selenides with activated carboxylic acid derivatives,^{10d,11a,12} reaction of trimethylsilyl selenocarboxylates with the fluoride anion,^{12b,13} nucleophilic deacylation of diacyl selenides^{10b,14} and diacyl diselenides,^{10c,15} or selenation of carboxylic acids^{10a,16} with Woollins' reagent.¹⁷ While these methods have proved adequate for the synthesis of simple selenocarboxylates, all suffer from problems associated with the lack of functional group compatibility or the use of unstable air-sensitive reagents.

By analogy with the generation of thiocarboxylates by elimination from *S*-(9-fluorenylmethyl)^{4c} or *S*-(2-cyanoethyl)³¹ thiocarboxylates, we conceived that the usefulness of selenocarboxylates in synthesis would be expanded by the availability of a general, clean method for their generation in situ from a readily accessible, stable derivative such as a *Se*-(9-fluorenylmethyl) selenocarboxylate. Toward this end we prepared the yellow, crystalline, and air-stable bis(9-fluorenylmethyl) diselenide **2** by reaction of 9-fluorenylmethyl tosylate **1** with the reagent generated in situ by the action of sodium borohydride on metallic selenium (Scheme 1).

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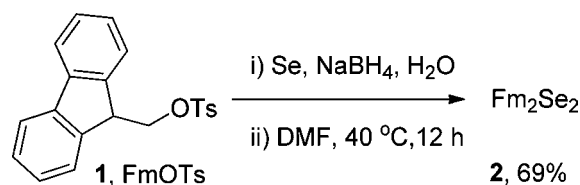
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Scheme 1. Preparation of Bis(9-fluorenylmethyl) Diselenide



Various amino acid based Fm selenoesters were then prepared by reduction of the diselenide **2** with sodium borohydride in ethanolic THF followed by reaction with *N*-Boc-protected aminoacyl *N*-hydroxysuccinimides (Table 1). These Fm selenoesters were isolated as white or off-white solids in good yield following chromatography over silica gel.

Table 1. Preparation of Fluorenylmethyl Selenoesters^a

Fm_2Se_2 2 <i>i</i>) NaBH₄, EtOH, THF <i>ii</i>) Boc-AA₁-OSu Boc-AA₁-SeFm 3-7		
entry	product	% yield
1	Boc-Phe-SeFm (3)	77
2	Boc-D-Phe-SeFm (4)	74
3	Boc-Val-SeFm (5)	81
4	Boc-Ala-SeFm (6)	75
5	Boc-Asp-(γ-SeFm)-OBn (7)	60

^a All AAs have the L-configuration unless otherwise indicated.

Subsequent treatment with trifluoroacetic acid in dichloromethane, followed by evaporation and trituration with ether, gave the corresponding ammonium salts as white solids (Table 2). Coupling with a *N*-Boc-protected amino acid with the aid of *O*-benzotriazolyl tetramethyluronium hexafluorophosphate (HBTU) in the presence of diisopropylethylamine (DIEA) then afforded a series of

Table 2. Boc Removal and Dipeptide Formation in the Presence of 9-Fluorenylmethyl Selenoesters^a

$\text{Boc-AA}_1\text{-SeFm} \xrightarrow[\text{CH}_2\text{Cl}_2]{\text{TFA,}} \text{TFA.H-AA}_1\text{-SeFm} \xrightarrow[\text{HBTU, DIEA, DMF}]{\text{Boc-AA}_2\text{-OH,}} \text{Boc-AA}_2\text{-AA}_1\text{-SeFm}$ 3-7 8-12 13-17						
entry	substrate	ammonium salt	% yield	Boc-AA ₂ -OH	dipeptide	% yield
1	Boc-Phe-SeFm (3)	TFA·Phe-SeFm (8)	94	Boc-Val-OH	Boc-Val-Phe-SeFm (13)	80
2	Boc-D-Phe-SeFm (4)	TFA·D-Phe-SeFm (9)	90	Boc-Val-OH	Boc-Val-D-Phe-SeFm (14)	81
3	Boc-Val-SeFm (5)	TFA·Val-SeFm (10)	95	Boc-Phe-OH	Boc-Phe-Val-SeFm (15)	88
4	Boc-Ala-SeFm (6)	TFA·Ala-SeFm (11)	94	Boc-Phe-OH	Boc-Phe-Ala-SeFm (16)	79
5	Boc-Asp-(γSeFm)-OBn (7)	TFA·Asp-(γSeFm)-OBn (12)	91	Boc-Val-OH	Boc-Val-Asp-(γSeFm)-OBn (17)	70

^a All AAs have the L-configuration unless otherwise indicated.

dipeptides in good yield (Table 2). The ability to remove the Boc-protecting group in this manner and conduct a subsequent peptide bond-forming reaction demonstrates the stability of the selenoester function toward acidic conditions and its reduced reactivity toward amines as compared to standard activated amino acid esters, as is also apparent from the recent solid-phase work of Durek et al.^{11b} Comparison of the ¹³C NMR spectra of the diastereomeric dipeptidyl selenoesters **13** and **14** revealed the absence of epimerization α- to the selenoester function in any of the three steps reported in Tables 1 and 2.

Table 3. Reaction of Fluorenylmethyl Selenoesters with Amines^a

entry	substrate	product	% yield
1	Boc-Phe-SeFm (3)	Boc-Phe-NC ₅ H ₁₀ (18)	70
2	Boc-Phe-SeFm (3)	Boc-Phe-NHBn (19)	87
3	Boc-Val-SeFm (5)	Boc-Val-NHBn (20)	72

^a All AAs have the L-configuration.

Attempted deprotection of the Fm selenoester **3** with piperidine in DMF, as previously employed for the Fm thioesters,^{4c} resulted only in the displacement of selenoester function giving only the piperidyl amide **18** (Table 3)

and confirming the high reactivity of selenoesters toward soft nucleophiles such as amines.¹⁸ Similar coupling reactions were also observed with benzylamine (Table 3). However, in light of the subsequently established reaction of amines with selenocarboxylates (Table 4) we cannot rule out the possibility of a two-stage mechanism for these reactions.

The apparent direct reaction of the selenoesters with basic amines was circumvented by the use of DBU as the base as also reported by Namelikonda and Manetsch for the analogous fluorenylmethyl thioesters.^{3k} The so-formed selenocarboxylates were not isolated but were immediately exposed to reaction with amino acid methyl esters in DMF at rt resulting in the formation of a series of dipeptides (Table 4). Beyond the simple amino acid derivatives of entries 1–3 of Table 4, entry 4 demonstrates application of this chemistry to the side chain of aspartic acid, while entry 5 establishes viability at the dipeptide level. The direct reaction of selenocarboxylates with amines to give amides in this manner is reminiscent of the analogous reaction of thiocarboxylates with amines reported by Wang and Danishefsky, and others, albeit they proceed in significantly better yield in the absence of additives such as HOBT.^{7n,p} We cannot rule out the possibility of a mechanism involving oxidation to the corresponding diacyl diselenides by extraneous air despite our best efforts to the contrary. However, in view of the

Table 4. Formation of Selenocarboxylates and Their Reaction with Amines^a

$\text{Boc-AA}_1\text{-SeFm} \xrightarrow[\text{DBU, DMF}]{} [\text{Boc-AA}_1\text{-Se}] \xrightarrow[\text{H-AA}_2\text{-OMe,}]{\text{21-24}} \text{Boc-AA}_1\text{-AA}_2\text{-OMe}$ 3, 5, 7, 15 21-24 25-29					
entry	substrate	selenocarboxylate ^b	H-AA ₂ OMe	product	% yield
1	Boc-Phe-SeFm (3)	Boc-Phe-Se [−] (21)	H-Val-OMe	Boc-Phe-Val-OMe (25)	64
2	Boc-Val-SeFm (5)	Boc-Val-Se [−] (22)	H-Leu-OMe	Boc-Val-Leu-OMe (26)	56
3	Boc-Val-SeFm (5)	Boc-Val-Se [−] (22)	H-D-Phe-OMe	Boc-Val-D-Phe-OMe (27)	64
4	Boc-Asp-(γSeFm)-OBn (7)	Boc-Asp-(γSe [−])-OBn (23)	H-Val-OMe	Boc-Asp-(γ-Val-OMe)-OBn (28)	78
5	Boc-Phe-Val-SeFm (15)	Boc-Phe-Val-Se [−] (24)	H-D-Phe-OMe	Boc-Phe-Val-D-Phe-OMe (29)	59

^a All AAs have the L-configuration unless otherwise indicated. ^b Selenocarboxylates were not isolated but used immediately in situ.

Table 5. Formation of Selenocarboxylates and Their Reaction with Various Electrophiles^a

$\text{Boc-AA}_1\text{-SeFm} \xrightarrow{\text{DBU, DMF}} [\text{Boc-AA}_1\text{-Se}^-] \xrightarrow{\text{electrophile}} \text{Boc-AA}_1\text{-X}$ 3, 5 21, 22 19, 30-33					
entry	substrate	selenocarboxylate ^b	electrophile	product	% yield
1	Boc-Val-SeFm (5)	Boc-Val-Se ⁻ (22)	PhCOCH ₂ Br	Boc-Val-SeCH ₂ COPh (30)	85
2	Boc-Phe-SeFm (3)	Boc-Phe-Se ⁻ (21)	Me ₂ NpC ₆ H ₄ N ₃	Boc-Phe-NHpC ₆ H ₄ NMe ₂ (31)	43
3	Boc-Phe-SeFm (3)	Boc-Phe-Se ⁻ (21)	MepC ₆ H ₄ SO ₂ N ₃	Boc-Phe-NHSO ₂ pC ₆ H ₄ Me (32)	65
4	Boc-Phe-SeFm (3)	Boc-Phe-Se ⁻ (21)	PhCH ₂ N ₃	Boc-Phe-NHCH ₂ Ph (19)	26
5	Boc-Phe-SeFm (3)	Boc-Phe-Se ⁻ (21)	PhN=C=O	Boc-Phe-NHPh (33)	48
6	Boc-Phe-SeFm (3)	Boc-Phe-Se ⁻ (21)	PhN=C=S	Boc-Phe-NHPh (33)	84
7	Boc-Val-SeFm (5)	Boc-Val-Se ⁻ (22)	PhN=C=S	Boc-Val-NHPh (34)	86

^a All AAs have the L-configuration. ^b Selenocarboxylates were not isolated but used immediately in situ.

acidity of hydrogen selenide (pKa1 3.89, pKa2 11.0) as compared to that of hydrogen sulfide (pKa1 6.88, pKa2 14.15) we consider it likely that selenide (Se²⁻) is a viable leaving group in this chemistry.

Finally, we turned our attention to the reaction of the in situ generated *N*-protected amino acyl selenocarboxylates with other electrophiles (Table 5). Thus, as anticipated in view of the precedent,^{10a,11a,12c} selenocarboxylates are alkylated by a simple alkyl halide to give selenoesters (Table 5, entry 1). *N*-Protected amino acyl selenocarboxylates react at rt with azides to give amides (Table 5, entries 2–4), as has been reported for simple selenocarboxylates,¹⁰ although at least for the present examples the reaction is noticeably more efficient with electron-deficient azides as is known to be the case for thiocarboxylates.^{3g} Finally, again analogously with the thiocarboxylates,^{5a,d} we demonstrate the reaction of selenocarboxylates with isocyanates and isothiocyanates to give amides (Table 5, entries 5–7).

Overall, we demonstrate that *Se*-(9-fluorenylmethyl) selenoesters are readily prepared, stable precursors to selenocarboxylates, which they liberate on treatment with DBU. The Fm selenoesters are compatible with the use of TFA for the removal of Boc groups and with simple peptide bond forming reactions. Amino acid derived selenocarboxylates condense directly with amines to give amides, react smoothly with isocyanates and isothiocyanates to give amides, and couple with electron-deficient azides also to give amides.

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Supporting Information Available. Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.