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Racemization in the Use of *N*-(9-(9-Phenylfluorenyl))Serine-Derived Cyclic Sulfamidates in the Synthesis of δ-Keto α-Amino Carboxylates and Prolines

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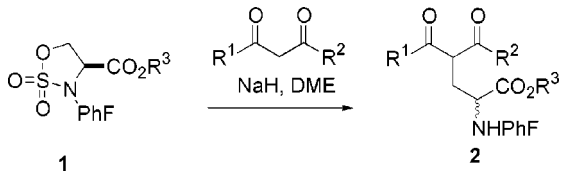
ABSTRACT



Ring opening of enantiopure *N*-(9-(9-phenylfluorenyl)serine-derived cyclic sulfamidates with β-keto esters, β-keto ketones, and dimethyl malonate gave a variety of γ-substituted amino acid analogues in racemic form. Investigation of the mechanism for racemization revealed that β-elimination occurred to form a dehydroalanine intermediate that underwent subsequent Michael addition.

In the context of our research in the fields of peptide mimicry[1−3] and excitatory amino acid synthesis,[4] we have made extensive use of aminodicarboxylate-derived β-keto esters.[1−8] Previously, β-keto esters were obtained via acylation of the ω-enolate of γ-methyl *N*-(PhF)glutamate derivatives (PhF = 9-(9-phenylfluorenyl)).[4−8] Although this method proved effective for synthesizing β-keto esters on variable scales depending on the electrophile, an alternative approach was sought that would be more amenable to large scale synthesis and library generation. We envisioned that a method based on ring opening of cyclic sulfamidates derived from serine could be used to prepare the desired β-keto esters and β-keto ketones.

Serine-derived cyclic sulfamidates have been effectively used as "β-alanyl cation" synthons for the synthesis of α-amino acids because the cyclic sulfamidate can simultaneously activate the β-position to nucleophilic attack and protect the amino group.[9−19] Several examples of nucleophilic

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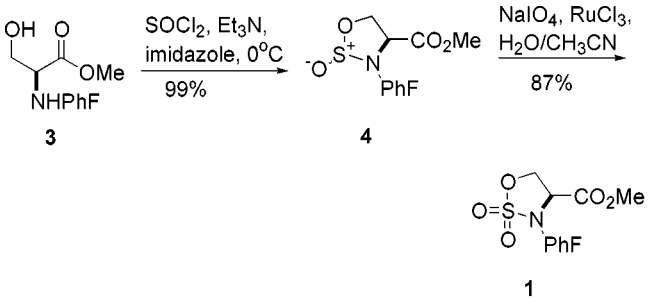
ring opening of cyclic sulfamidates derived from serine have been described with nitrogen,[9−14] oxygen,[9−11,14,15] sulfur,[9,11,14] and fluoride[11,13,17−19] nucleophiles. On the other hand, ring-opened products have rarely been synthesized with carbon nucleophiles[16a] other than cyanide.[9,11,13,16a] An exception to this trend was the ring opening of (4*S*)-*tert*-butyl 2,2-dioxo-3-benzyl-1,2,3-oxathiazolidine-4-carboxylate with diethyl malonate which produced *tert*-butyl *N*-benzyl-4-ethoxycarbonyl pyroglutamate as well as a dehydroalanine side product.[9] Attempting to extend this reactivity with carbon nucleophiles, we have studied *N*-(PhF)serine-derived cyclic sulfamidate **1** and have discovered a β-elimination/Michael addition pathway that furnished racemic γ-substituted amino acid products.

(4*S*)-Methyl 2,2-dioxo-3-PhF-1,2,3-oxathiazolidine-4-carboxylate (**1**) was synthesized in two steps from *N*-(PhF)-serine methyl ester **3** (Scheme 1).[20] Treatment of serine **3**

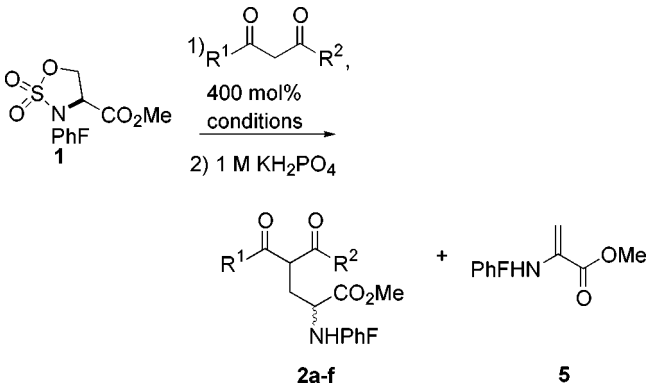
Scheme 1. Synthesis of *N*-(PhF)Serine-Derived Cyclic Sulfamidate **1**



with thionyl chloride, triethylamine, and imidazole in dichloromethane furnished quantitatively a 1:2 mixture of diastereoisomeric sulfamidites **4** that could be separated by chromatography on silica gel using an eluent of EtOAc in hexane.[21] Subsequent oxidation of sufamidites **4** with sodium periodate and catalytic ruthenium trichloride in acetonitrile and water at 0 °C afforded cyclic sulfamidate **1** in 86% overall yield.[22]

Ring opening of sulfamidate **1** was examined under various conditions using enolates derived from β-keto esters, β-keto ketones, and dimethyl malonate as nucleophiles (Scheme 2).

Scheme 2. Synthesis of γ-Acyl Amino Acids **2** by Ring Opening of Cyclic Sulfamidate **1**



We found that the desired amino acid derivatives **2** were best prepared on treatment of sulfamidate **1** with a premixed solution containing 400 mol % of β-keto ester or β-keto ketone and 220 mol % of sodium hydride in DME, followed by heating at 60 °C for 18 h and cooling to room temperature before hydrolysis of the reaction mixture with 1 M KH_2PO_4 and chromatography (Table 1).[23] Dehydroalanine **5** was also encountered as a significant side product.

β-Keto esters **2a** and **2c** were respectively converted to 5-methylproline[24,25] and δ-keto α-amino ester **6c**,[6] an intermediate in the synthesis of *N*-BOC-5-*tert*-butylproline **8c** (Scheme 3). Hydrolysis and decarboxylation of β-keto esters

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(21) **(2*R*,4*S*)-Methyl 2-Oxo-3-(PhF)-1,2,3-oxathiazolidine-4-carboxylate ((2*R*)-4) and (2*S*,4*S*)-Methyl 2-Oxo-3-(PhF)-1,2,3-oxathiazolidine-4-carboxylate ((2*S*)-4).** A solution of *N*-PhF-L-serine methyl ester ((*S*)-**3**, 3.57 g, 10 mmol, prepared according to ref 20) in 150 mL of dichloromethane was cooled to 0 °C, treated with imidazole (2.7 g, 40 mmol) followed by triethylamine (2.8 mL, 20 mmol), stirred for 10 min, and then treated with thionyl chloride (0.8 mL, 11 mmol). After stirring an additional 45 min, water (100 mL) was added and the phases were separated. The aqueous phase was extracted with dichloromethane (3 × 50 mL), and the combined organic fractions were washed with water (2 × 50 mL), dried, filitered, and evaporated. The residue was normally used without purification in the next reaction. Purification of the residue by chromatography on silica gel with an eluant of 20−30% EtOAc in hexane provided 4 g (99%) of a 1:2 mixture of diastereomers, (2*R*)-**4** and (2*S*)-**4**. First to elute was (2*R*)-**4**: TLC R_f = 0.54 (30% EtOAc in hexanes); mp 83−84 °C; $[\alpha]^{20}_D$ 121° (*c* 0.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42 (s, 3 H), 3.51 (dd, 1 H, *J* = 1.4, 7.1), 4.41 (dd, 1 H, *J* = 1.4, 9.4), 4.75 (dd, 1 H, *J* = 7.1, 9.4), 7.17−8.17 (m, 13 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.1, 59.0, 72.2, 75.2, 171.4; HRMS calcd for $C_{23}H_{20}O_4NS$ (MH^+) 406.1113, found 406.1130. Next to elute was (2*S*)-**4**: TLC R_f = 0.37 (30% EtOAc in hexanes); mp 71−72 °C; $[\alpha]^{20}_D$ 243° (*c* 0.38, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (t, 1 H, *J* = 7.9), 3.57 (s, 3 H), 4.32 (t, 1 H, *J* = 7.9), 4.95 (t, 1 H, *J* = 7.9), 7.19−7.77 (m, 13 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.5, 61.3, 73.5, 76.2, 170.3; HRMS calcd for $C_{23}H_{19}O_4NS$ (M^+) 405.1035, found 405.1046. Stereochemistry was ascertained by a combination of NMR spectroscopy and X-ray crystallography experiments to be reported in a forthcoming manuscript in preparation.

(22) **(4*S*)-Methyl 2,2-Dioxo-3-PhF-1,2,3-oxathiazolidine-4-carboxylate (1).** A solution of 2-oxo-1,2,3-oxathiazolidine **4** (1.25 g, 3.1 mmol) in 100 mL of acetonitrile was cooled to 0 °C, treated with ruthenium(III) chloride monhydrate (10 mg) followed by sodium periodate (1.28 g, 6 mmol), stirred for 10 min, and quenched with water (100 mL). After stirring for 4 h, the reaction mixture was diluted with ether (100 mL) and the phases were separated. The aqueous phase was extracted with ether (3 × 60 mL). The combined organic fractions were washed with saturated aqueous sodium bicarbonate (100 mL) and brine (50 mL), dried, filtered, and evaporated to a residue that was purified by chromatography on silica gel with an eluant of 0−20% EtOAc in hexane. Evaporation of the collected fractions provided 1.14 g (87%) of **1**: mp 155−156 °C; $[\alpha]^{20}_D$ 244° (*c* 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (dd, 1 H, *J* = 4.0, 8.2), 3.69 (s, 3 H), 4.02 (dd, 1 H, *J* = 8.2, 8.7), 4.38 (dd, 1 H, *J* = 4.0, 8.7), 7.19−8.22 (m, 13 H); ^{13}C NMR (75 MHz, $CDCl_3$) (52.9, 58.8, 66.8, 77.9, 169.2; HRMS calcd for $C_{23}H_{19}O_5NS$ (M^+) 421.0984, found 421.0997.

(23) **General Procedure for Ring Opening of Five-Membered Cyclic Sulfamidates with β-Keto Esters, β-Keto Ketones, and Dimethyl Malonate.** A solution of sodium hydride (prewashed with hexane, 60 wt % in oil, 85 mg, 2.1 mmol) in DME (15 mL) was treated with the respective β-keto ester, β-keto ketone, or dimethyl malonate (3.6 mmol), stirred for 10 min, treated with (4*S*)-methyl 2,2-dioxo-3-PhF-1,2,3-oxathiazolidine-4-carboxylate (**1**, 380 mg, 0.9 mmol), heated at 60 °C for 18 h, cooled to room temperature, and poured into 1 M NaH_2PO_4 (50 mL). The mixture was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (2 × 30 mL), dried, filtered, and evaporated to a residue. Isolation protocols as well as spectral characterization data for **2a**−**f** are presented in the Supporting Information.

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Table 1. Synthesis of γ-Acyl Amino Acids **2** by Ring Opening of Cyclic Sulfamidate **1** with Enolates of β-Keto Ester, β-Keto Ketone, and Dimethyl Malonate

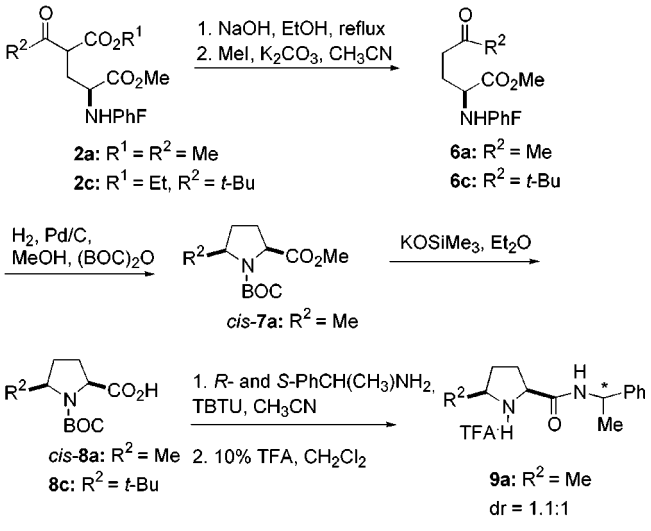
	nucleophile				
entry	R^1	R^2	conditions	**2**[a] (%)	**5** (%)
a	Me	OMe	K_2CO_3, DMF, rt, 3 d		100[c]
	Me	OMe	K_2CO_3, THF, rt, 3 d	30[b]	*d*
	Me	OMe	Cs_2CO_3, THF, rt, 5 d		100[c]
	Me	OMe	K_3PO_4, DME, rt, 18 h	43[b]	*d*
	Me	OMe	NaH, THF, 60 °C, 6 h	51[b]	
	Me	OMe	NaH, DME, 60 °C, 4 h	67[b]	
	Me	OMe	NaH, DME, 60 °C, 18 h	86[b]	
b	Et	OEt	NaH, DME, 60 °C, 18 h	82	
c	*t*-Bu	OEt	NaH, DME, 60 °C, 18 h	63	
d	Me	Me	NaH, DME, 60 °C, 18 h	66[b]	*d*
e	Ph	Me	NaH, DME, 60 °C, 18 h	45	
f	OMe	OMe	NaH, DME, 60 °C, 18 h	65[b]	

[a] Isolated yield. [b] Caculated yield from an isolated mixture of **2** and β-dicarbonyl starting material. [c] Determined by ^{1}H NMR spectroscopy. [d] Observed by TLC.

2a and **2c** with sodium hydroxide in ethanol heated at a reflux provided their respective δ-oxo-α-*N*-(PhF)amino acids that were esterified with iodomethane and potassium carbonate in acetonitrile to provide respectively methyl 5-oxo-2-[*N*-(PhF)amino]hexanoate (**6a**) and methyl 6,6-dimethyl-5-oxo-2-[*N*-(PhF)amino]heptanoate (**6c**).[6] Hydrogenation of δ-oxo-heptanoate **6a** with palladium-on-carbon and di-*tert*-butyl dicarbonate in methanol proceeded by cleavage of the PhF protection, *N*-acylation, imine formation, and hydrogenation to furnish *N*-(BOC)-5-methylproline methyl ester **7a** as the *cis*-diastereomer. Hydrolysis of methyl ester *cis*-**7a** with potassium trimethylsilanolate in Et_2O furnished *N*-(BOC)-5-methylproline *cis*-**8a** in 96% yield.

The enantiomeric purity of *cis*-*N*-(BOC)-5-methylproline (*cis*-**8a**) was ascertained by spectral analysis of its diastereomeric α-methylbenzylamides **9a**, which were synthesized by coupling *cis*-*N*-(BOC)-5-methylproline **8a** to L- and D-α-methylbenzylamine followed by removal of the BOC group with 10% TFA in CH_2Cl_2 (Scheme 3). In the ^{1}H NMR spectra of α-methylbenzylamides **9a**, the disteromeric methyl doublet peaks were resolved and came at 1.50 and 1.49 ppm, as well as at 1.46 and 1.42 ppm. Integration of these doublets indicated that **9a** was of only 10% diasteromeric excess.

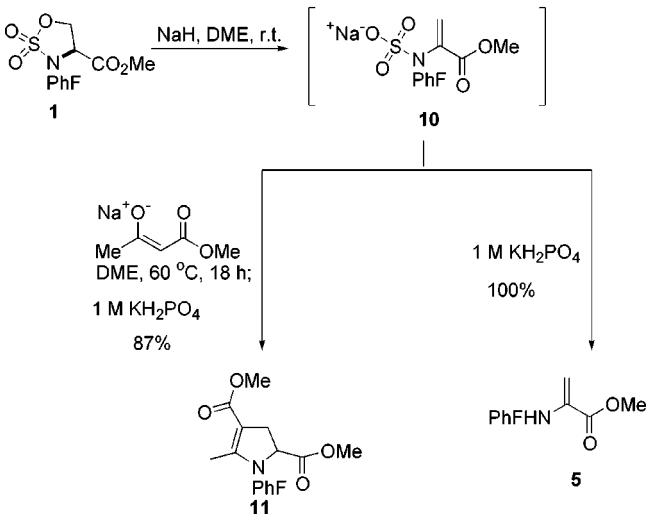
Scheme 3. Synthesis and Enantiomeric Purity of 5-Alkylprolines **8**



Racemization had evidently occurred during the synthesis of *cis*-*N*-(BOC)-5-methylproline **8a**. The cause of this loss of configurational integrity was narrowed down to the ring-opening step by subsequent investigation of the purity of heptanoate **6c**. Measurement of the specific rotation of δ-keto α-amino ester **6c** showed a considerable drop in optical purity ($[\alpha]^{20}_D$ −1.2° (*c* 0.8, $CHCl_3$); lit.[6] $[\alpha]^{20}_D$ −137.7° (*c* 1, MeOH)). Because hydrolysis and decarboxylation of β-keto ester **2c**, prepared from a route featuring acylation of *N*-(PhF)glutamate γ-methyl ester,[5] produced enantiopure **6c** ($[\alpha]^{20}_D$ −139.2° (*c* 0.8, MeOH)), we considered that racemization occurred prior to or during the nucleophilic addition to cyclic sulfamidate **1** and not at the hydrolysis and decarboxylation steps. In addition, the low specific rotation value ($[\alpha]^{20}_D$ −9.0° (*c* 0.15, $CHCl_3$)) for glutamate **2f** also suggested loss of configurational integrity during additon of dimethyl malonate to cyclic sulfamidate **1**.

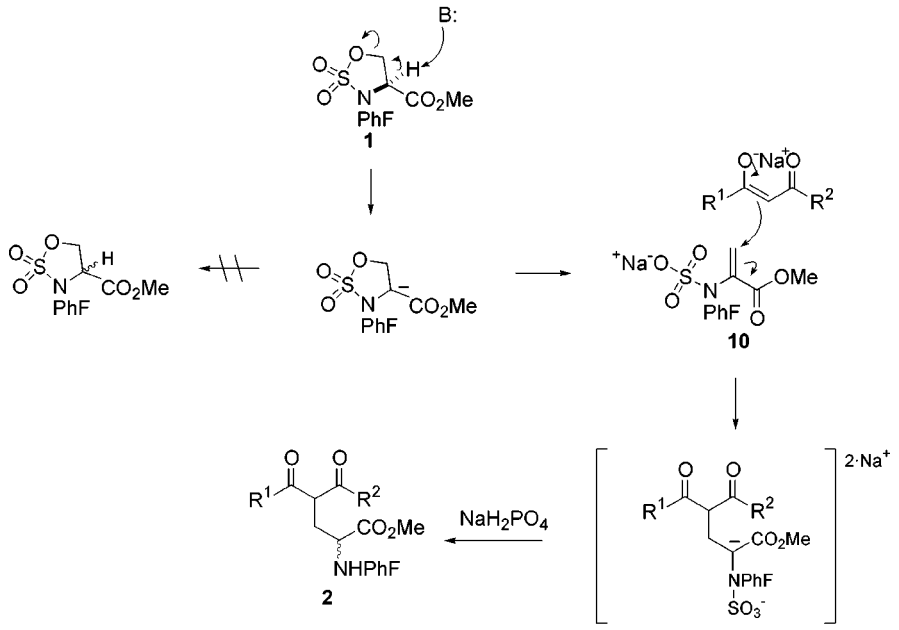
Because dehydroalanine intermediates were detected during the reactions of five-member cyclic sulfamidate **1**, we synthesized dehydroalanine **5** by β-elimination induced with sodium hydride as a poor nucleophile (Scheme 4). We next

Scheme 4. Michael Addition of Methyl Acetoacetate Enolate to Dehydroalanine Sulfamic Acid **10**



tried to determine if the presumed dehydroalanine intermediate **10** could serve as a Michael acceptor for the formation of racemic β-keto ester. Sulfamidate **1** was treated with 300 mol % of sodium hydride in DME to form the elimination product **10**. Treatment of **10** with a premixed solution of methyl acetoacetate (300 mol %) and NaH (400 mol %) in DME, heating at 60 °C for 18 h, followed by hydrolysis of

Scheme 5. Proposed Mechanism for the Ring Opening of Sulfamidate **1** with β-Keto Ester



the polar sulfamic acid intermediate with 1 M KH_2PO_4, furnished (5*RS*)-methyl *N*-PhF-2-methyl-3-(methyloxy)carbonyl-Δ^2-pyrroline (**11**) in 87% yield (Scheme 4). Previously, we encountered pyrroline **11** in the direct ring opening of sulfamidate **1** with the preformed enolate of methyl acetoacetate when the hot reaction mixture was quenched with 1 M KH_2PO_4. Although formation of **11** can be avoided by cooling the reaction mixture to room temperature prior to hydrolysis of the sulfamic acid, we elected to form **11** in this sequence because it was easier to characterize. The formation of **11** demonstrated thus that dehydroalanine **10** could serve as a prochiral intermediate for the formation of racemic **2**. To verify if sulfamidate **1** racemized prior to ring opening, we removed aliquots of the reaction mixture containing **1** and the preformed sodium enolate of methyl acetoacetate in DME at 60 °C. No loss of configurational integrity of sulfamidate **1** was observed after 1 and 2 h of reaction as determined by measurement of its specific rotation after isolation by chromatography. Hence, α-deprotonation triggers β-elimination prior to reprotonation and racemization of **1**.

A mechanism that may explain the cause of this racemization involves α-proton removal to trigger ring opening with elimination. Preliminary experiments indicate that elimination may be induced by residual base or by the enolate itself. Enolate may then attack **10** by a Michael addition to furnish after workup β-keto ester **2** (Scheme 5).[26] Further investigations are now in progress to define the scope and limitations of *N*-(PhF)serine-derived sulfamidates as configurationally labile chiral educts.

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Supporting Information Available: Descriptions of experimental procedures and spectral data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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