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N-Thioacylation of β–Amino Alcohols by *N*-(Thioacyl)phthalimides: A Facile Synthesis of α–Amino Acid Thiazolines

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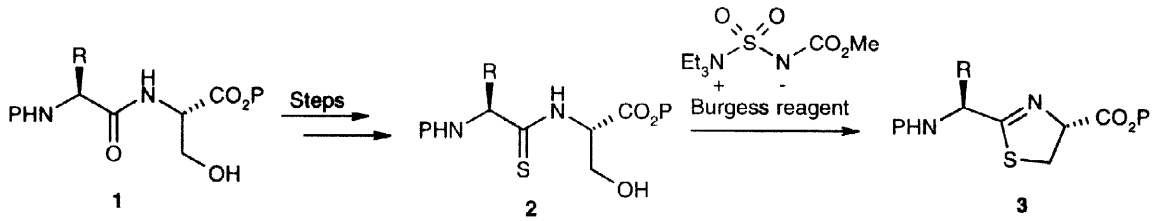
Abstract: β–amino alcohols are selectively *N*-thioacylated by *N*-(thioacyl)phthalimides under very mild conditions to provide *N*-(hydroxyethyl)thioamides in high yields. Cyclodehydration with Burgess reagent then provides α–amino acid thiazolines. This approach provides a convenient alternative to those based upon thionation of a preformed *N*-(hydroxyethyl)amide.

The thiazoline ring system occurs as a modified peptide linkage in a variety of biologically active natural products, particularly of marine origin.[1] Studies towards the total synthesis of these compounds have prompted an interest in approaches to stereodefined peptide thiazolines.[2] Of particular synthetic value has been the procedure based on cyclodehydration of *N*-(hydroxyethyl)thiodipeptides by Burgess reagent,[3] Scheme 1, which provides peptide thiazolines, *e.g.* **3**, in high stereochemical purity (<3% epimerization).[2d] The intermediate *N*-(hydroxyethyl)thiodipeptides **2** have hitherto been prepared in several steps from the pre-formed dipeptides **1** *via* *O*-silyl protection, thionation using Lawesson's reagent, and *O*-desilylation.[2b,c] Alternatively, cyclodehydration of compounds **1** with Burgess reagent provides oxazolines which may be transformed into compounds **2** by thiolysis at the C(2) position, using H_2S/MeOH/Et_3N.[2e-g]



Scheme 1

A more convergent approach to generalized *N*-(hydroxyethyl)thioamides **5** would proceed in a single step by direct *N*-thioacylation of an unprotected β–amino alcohol, as shown in Scheme 2. We recently introduced *N*-(thioacyl)phthalimides **4** as efficient *N*-thioacylating agents.[4] These compounds are readily obtained in high enantiomeric purity from the corresponding protected amino acid amides *via* an efficient, two-step thionation-

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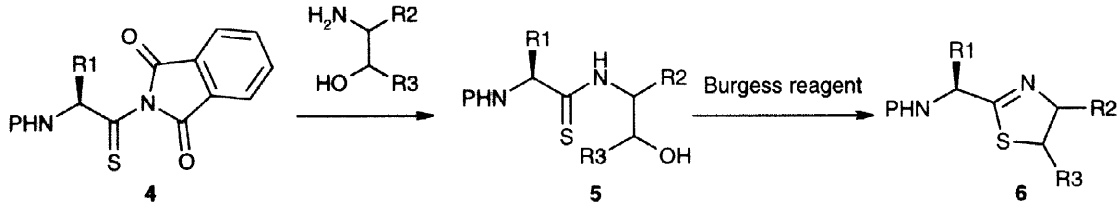
activation sequence, and react with amine nucleophiles under mild conditions to provide high yields of thioamides. In addition, we noted that treatment of amino alcohols with *N*-(thioacyl)phthalimides **4** provided exclusively the *N*-thioacylated products, thus avoiding the need for *O*-protection. Herein we describe a facile synthesis of the generalized amino acid thiazolines **6**, which incorporates *N*-thioacylation of β–amino alcohols as the key step.



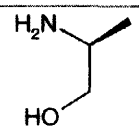
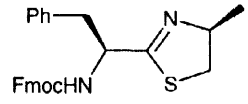
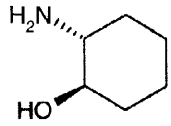
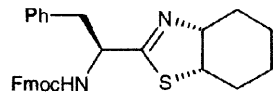
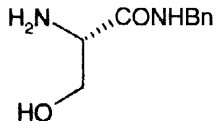
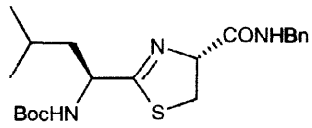
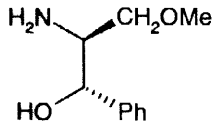
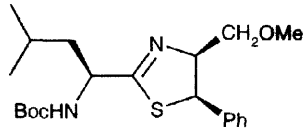
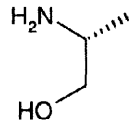
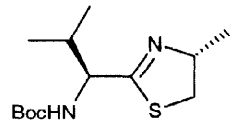
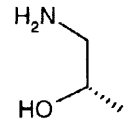
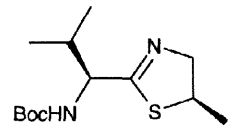
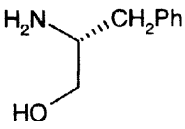
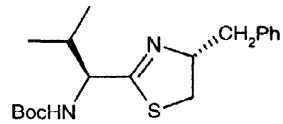
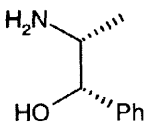
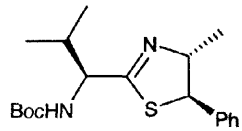
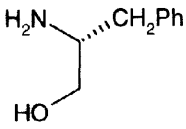
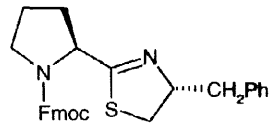
Scheme 2

A range of of *N*-(thioacyl)phthalimides **4** was treated with a selection of β–amino alcohols. The resulting *N*-(hydroxyethyl)thioamides **5** were subjected to Burgess reagent to generate the thiazolines **6**. The results are summarized in the **Table**.

The *N*-(thioacyl)phthalimides **4** reacted smoothly with the amino alcohols under very mild conditions ($CHCl_3$, 0 °C) and provided the *N*-(hydroxyethyl)thioamides **5** in good to excellent yields as the only thioacylation products. The reactions were essentially instantaneous as indicated by the immediate discharge of the orange colour due to the thioacylating agents.[5] In entry 5 the diastereomeric purity of the *N*-(hydroxyethyl)thioamide product was 98.3%, as determined by HPLC comparison with the diastereoisomer formed from the enantiomeric β–amino alcohol. Reactions of the valine-derived thioacylating agent, entries 5-8, proceeded efficiently with no significant retardation due to steric hindrence. However, it was noted that treatment of the hindered β–amino alcohol 1-amino-1-cyclopentanemethanol with Boc-Leuψ[CSN]Pht failed to provide any of the expected *N*-thioacylation product.

Cyclization of the *N*-(hydroxyethyl)thioamides **5** by treatment with Burgess reagent in THF proceeded cleanly in good to excellent yields. Reactions in which ring closure takes place at a primary alcohol were complete within 1.25 h at room temperature, see **Table**, odd-numbered entries. Cyclization of the secondary alcohols required heating to 50 °C for 1 h, see **Table**, even-numbered entries. The stereochemical purities of the thiazoline products in entries 5 and 6 were confirmed by comparison of their ^1H NMR spectra with those of the diastereoisomers derived from the enantiomeric β–amino alcohols. In each case the diastereomeric purity was determined to be >95%. The *N*-thioacylation-cyclodehydration sequence may conveniently be carried out without isolation of the intermediate *N*-(hydroxyethyl)thioamide. In entry 4, the crude *N*-(hydroxyethyl)thioamide was treated directly with Burgess reagent in THF; evaporation and filtration through silica gel gave the pure thiazoline.

Table: Data for the Synthesis of *N*-(Hydroxyethyl)thioamides 5 and Thiazolines 6

Entry	*N*-(Thioacyl)phthalimide **4**	β–Amino alcohol	Yield of **5** (%)[a]	Thiazoline **6**	Yield of **6** (%)[a]
1	Fmoc-Pheψ[CSN]Pht		91		91
2[b]	Fmoc-Pheψ[CSN]Pht		90		87
3	Boc-Leuψ[CSN]Pht		94		84
4	Boc-Leuψ[CSN]Pht		-[c]		77[d]
5	Boc-Valψ[CSN]Pht		81		88
6	Boc-Valψ[CSN]Pht		70		85
7	Boc-Valψ[CSN]Pht		80		77
8	Boc-Valψ[CSN]Pht		74		78
9	Fmoc-Proψ[CSN]Pht		77		85

[a]Yields of products isolated after flash chromatography; mass spectral, infra red and ^{1}H NMR data obtained for compounds **5** and **6** were consistent with the assigned structures. [b]Racemic *trans*-2-aminocyclohexanol was used, hence diastereomeric products were obtained. [c]The *N*-(hydroxyethyl)thioamide was not isolated. [d]Overall yield for the *N*-thioacylation-cyclodehydration sequence.

In summary, we provide an efficient synthesis of *N*-(hydroxyethyl)thioamides **5**, and hence α–amino acid thiazolines **6**, by use of *N*-(thioacyl)phthalimides as *N*-thioacylating agents. This method has advantages of synthetic convergency and experimental simplicity. In particular, the problem of introducing sulphur into a preformed *N*-(hydroxyethyl)amide is avoided.

References and Notes

1. For representative examples see: (a) Davidson, B.S. *Chem. Rev.* 1993, *93,* 1771-1791. (b) Wipf, P. *Chem. Rev.* **1995,** *95,* 2115-2134.(c) Wipf, P. *Synlett,* **1997,** 1-10.

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5. Example procedures (**Table**, entry 5): (a) To a stirred, ice-cooled solution of (*R*)-(-)-2-amino-1-propanol (24.1 mg, 0.32 mmol) in chloroform (2 ml) was added, dropwise, a solution of Boc-Valψ[CSN]Pht (71.1 mg, 0.196 mmol) in chloroform (1 ml). The orange colour due to the thioacylating agent was discharged immediately upon addition. After warming to room temperature (10 min), the reaction mixture was diluted with chloroform and washed with 10% aqueous citric acid then brine. Drying (Na_2SO_4) and rotary evaporation provided the crude product which was purified by flash chromatography (SiO_2, hexane/ethyl acetate 1/1) to afford the *N*-(hydroxyethyl)thioamide as a colourless foam (46.1 mg, 0.159 mmol, 81%) IR (KBr) 3292, 1707, 1508, and 1161 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 0.93 (d, *J* = 6 Hz, 3 H, CH_3) overlapping 0.98 (d, *J* = 6 Hz, 3 H, CH_3), 1.27 (d, *J* = 6 Hz, 3 H, CH_3), 1.44 (s, 9 H, *t*-Bu), 2.17 (m, 1 H, C*H*$(CH_3)_2$), 3.57 (dd, *J* = 5, 10 Hz, 1 H, C*H*HOH), 3.88 (dd, *J* = 4, 10 Hz, 1 H, CH*H*OH) overlapping 3.95 (m, 1 H, CHCS), 4.76 (m, 1 H, C*H*$(CH_3)CH_2OH$), 5.37 (br d, *J* = 7.5 Hz, 1 H, CONH), 8.36 (br s, 1 H,CSNH); *m/z* (FAB) 291 (M^+ + 1, 34%) and 235 (100).

(b) To a stirred solution of the above thioamide (46.0 mg, 0.159 mmol) in THF (2ml) was added Burgess reagent (44 mg, 0.185 mmol) and the reaction mixture was stirred for 1.25 h at room temperature. The reaction mixture was concentrated *in vacuo* and the resulting suspension was filtered through a short column of silica (hexane/ethyl acetate 1/1) to provide the thiazoline as a colourless oil (38.3 mg, 0.141 mmol, 88%) IR (evaporated film) 3330, 1716, 1623, 1495, 1366, and 1172 cm^{-1}.^1H NMR (200 MHz, $CDCl_3$) 0.88 (d, J = 6 Hz, 3 H, CH_3), 0.99 (d, J = 6 Hz, 3 H, CH_3), 1.32 (d, J = 6 Hz, 3 H, CH_3), 1.46 (s, 9 H, *t*-Bu), 2.13 (m, 1 H, C*H*$(CH_3)_2$), 2.92 (dd, *J* = 6, 10 Hz, 1 H, C*H*HS), 3.42 (dd, *J* = 8, 10 Hz, 1 H, CH*H*S), 4.40 (br m, 1 H, CHCNS), 4.58 (m, 1 H,C*H*(CH_3)N), 5.18 (br s, NH); *m/z* (FAB) 273 (M^+ + 1, 100%).