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Titanium(IV)-Mediated Tandem Deprotection–Cyclodehydration of Protected Cysteine *N*-Amides: Biomimetic Syntheses of Thiazoline- and Thiazole-Containing Heterocycles

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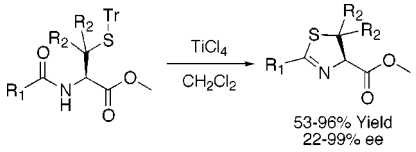
ABSTRACT



R_1 = Aryl or Alkyl; R_2 = H or Me; Tr = trityl

The scope and limitations of $TiCl_4$-mediated Δ^2-thiazoline synthesis via tandem deprotection–dehydrocyclization of trityl-protected cysteine *N*-amides is presented. While chemical yields are acceptable (53–96%), the stereochemical outcomes vary on the basis of structural considerations and reaction conditions (22–99% ee). Racemization at the C(2)-exomethine position limits the utility of this method for the formation of a thiazoline within a peptide. Treatment of a tritylated Cys-Cys dipeptide with $TiCl_4$ afforded the corresponding thiazole–thiazoline heterocycle 12 (38% yield, 97% ee).

Thiazoline and thiazole rings are structural motifs found in numerous natural products.[1] Their wide range of antitumor, antiviral, and antibiotic activities, as well as their ability to bind to proteins, DNA, and RNA, has fueled numerous synthetic and biological investigations.[2] The biosynthesis of thiazolines appears to involve an attack by the cysteine's sulfur on the enzyme-activated amide carbonyl group of the preceding residue.[3] While dehydration of the resulting tetrahedral intermediate affords a thiazoline ring, further oxidation is required to give the corresponding thiazole.

[†] P.R. and H.R. contributed equally to this work.

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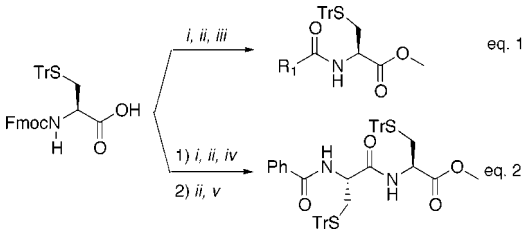
Over the years, a number of amino acid-based syntheses of Δ^2-thiazolines have been reported.[2a,b,d,e,h,j−o,4] Notably, Heathcock has used $TiCl_4$ to synthesize 4-carboxy-4-methyl-Δ^2-thiazolines from their corresponding α-methyl cysteine derivatives via amide bond activation.[2a,d,e,g] As part of a program directed at developing and applying biomimetic methods (i.e., amide bond activation) for the syntheses of peptide-derived heterocycles, we have investigated the scope and limitations of $TiCl_4$–mediated thiazoline ring formation with racemization-prone precursors.

Efficiency in organic synthesis is important.[5] Thus, reaction conditions that remove sulfur protecting groups and mediate cyclodehydration of cysteines to thiazolines are highly desirable. Since trityl groups (Tr) are removed under mild acidic conditions, oxophilic Lewis acids should effect the desired tandem deprotection−heterocyclization.

To test this, fully protected cysteine derivative **1** was synthesized (Scheme 1, eq 1) and treated with a variety of

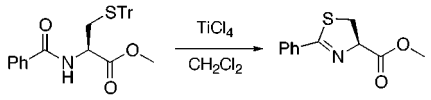
Scheme 1[a]



[a] Reagents: (i) $TMSCHN_2$, MeOH:C_6H_6; (ii) Et_2NH, CH_3CN; (iii) R_1COCl (see tables for the structures of R_1), DIEA, CH_2Cl_2; (iv) Fmoc-L-Cys(Tr)-OH, HBTU, HOBT, collidine, DMF:CH_2Cl_2; (v) PhCOCl, DIEA, CH_2Cl_2. Tr = trityl.

oxophilic Lewis acids. While most Lewis acids successfully removed the trityl group, only $TiCl_4$ mediated both *S*-deprotection and cyclodehydration (Scheme 2).[6]

Scheme 2



A summary of the reaction conditions used for the synthesis of thiazoline **2** from **1** is presented in Table 1.

Table 1. Dehydrocyclization of **1** Mediated by $TiCl_4$[a]

entry	temp (°C)	time (h)	yield (%)	% ee[b]
1	25	2	81	80
2	0	4	58	88
3	0	11	72	87
4	0	18	83	88

[a] Reactions were carried out using 3 equiv of $TiCl_4$ in CH_2Cl_2. [b] Enantiomeric excesses determined by chiral HPLC equipped with a photodiode array detector and a Chiralcel OD column.

Thiazoline **2** was afforded in good yield with significant racemization at 25 °C (entry 1, 81% yield, 80% ee). The reaction proceeded more slowly at 0 °C; after 18 h, a yield of 83% was realized with enhanced stereoselectivity at C(4) (entry 4, 88% ee). Since product enantiomeric purity measured as a function of reaction progress was almost invariant, it appears that a partial loss of chirality occurs during cyclodehydration (entries 2−4). This hypothesis is supported by the fact that resubjecting product **2** to the reaction conditions did not compromise its stereochemical integrity.

To further probe the scope of this reaction, protected cysteine *N*-amides **3**−**6** were synthesized (Scheme 1, eq 1). Titanium(IV)-mediated tandem deprotection−dehydrocyclization reactions of **3**−**6** proceeded in moderate to excellent yields (Table 2). The reaction with penicillamine analogue **3** afforded the highest chemical and optical yield, likely due to the Thorpe−Ingold effect which increases the rate of cyclization relative to competing racemization (entry 2; 96% yield, 99% ee).[7]

A substituent effect was observed for the cyclodehydration reactions of *N*-benzoylated starting materials (Table 2, entries 2 and 3). As expected, the presence of an electron-withdrawing substituent (i.e., *p*-NO_2) increased reactivity, while an electron-donating substituent (i.e., *p*-OMe) decreased it (77% vs 28% yield). Moreover, racemization was suppressed by the presence of an electron-donating group and enhanced by an electron-withdrawing group. This can be rationalized on the basis of the contribution of these substituents to the reduced or the increased acidity of the α-protons.

To ascertain the feasibility of one-pot multiple dehydrocyclizations, a fully protected Cys-Cys dipeptide was syn-

(3) For a recent review, see: Sinha Roy, R.; Gehring, A. M.; Milne, J. C.; Belshaw, P. J.; Walsh, C. T. *Nat. Prod. Rep.* **1999**, *16*, 249−263.

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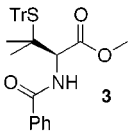
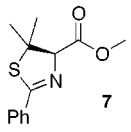
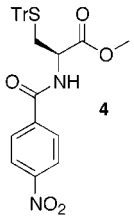
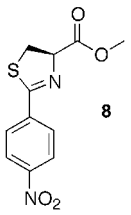
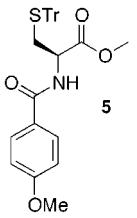
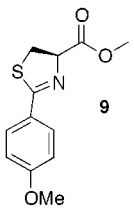
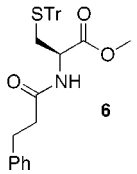
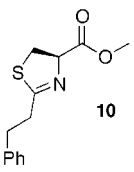
(5) Hudlicky, T.; Natchus, M. G. *Org. Synth.: Theory Appl.* **1993**, *2*, 1−25.

(6) **Typical experimental procedure:** A solution of *S*-trityl-protected cysteine *N*-amide **1** (0.125 mmol) in dry CH_2Cl_2 (2.5 mL) was treated with $TiCl_4$ (375 μL of a 1.0 M solution in CH_2Cl_2, 0.375 mmol) and stirred at 0 °C for 18 h. The reaction mixture was quenched with cold saturated aqueous $NaHCO_3$ (2×). The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The resultant crude product was purified by flash chromatography (30% EtOAc/hexanes) to afford **2** as a colorless oil (23.0 mg, 0.104 mmol, 83%). Data for **2**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88−7.26 (m, 5H, Ar), 5.29 (ABX, 1H, J_{AX} = 9.0, J_{BX} = 9.4 Hz, C*H*-N), 3.84 (s, 3H, O-C*H*$_3$), 3.72 (ABX, 1H, J_{AB} = 11.2, J_{AX} = 9.0 Hz, C*H*-S), 3.64 (ABX, 1H, J_{AB} = 11.2, J_{BX} = 9.4 Hz, C*H*-S); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 171.0, 132.6, 131.7, 128.6, 128.5, 78.5, 52.8, 35.3; HRMS (MALDI-FTMS) calcd for $C_{11}H_{12}NO_2S$ (M + H^+) 222.0589, found 222.0591.

(7) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, 1080.

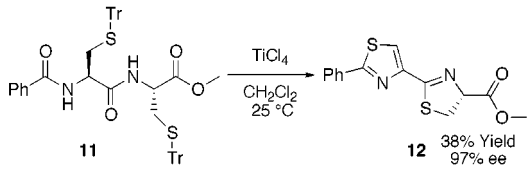
Table 2. Dehydrocyclization of Protected Cysteine Analogues Mediated by $TiCl_4$

Entry	Reactant	Product	Yield %[a] (% ee)[b]
1	 **3**	 **7**	96(99)[c]
2	 **4**	 **8**	77(22)
3	 **5**	 **9**	28(94) 51(93)[d]
4	 **6**	 **10**	61(91)

[a] Reactions were carried out using 3 equiv of $TiCl_4$ at 0 °C for 18 h. [b] Enantiomeric excesses determined by chiral HPLC equipped with a photodiode array detector and a Chiralcel OD column. [c] The reaction was carried out using 3 equiv of $TiCl_4$ at 0 °C for 4 h. [d] The reaction was carried out using 3 equiv of $TiCl_4$ at 25 °C for 11 h. Tr = trityl.

thesized (Scheme 1, eq 2). Reaction of Cys-Cys dipeptide **11** with $TiCl_4$ proceeded at 25 °C with the desired bis-deprotection−dehydrocyclization (Scheme 3). Interestingly,

Scheme 3



the reaction efficiently produced the corresponding thiazole−thiazoline heterocycle **12** (38% yield, 97% ee, >99% ee after a single crystallization). Single-crystal X-ray analysis of bis-heterocycle **12** confirmed the absolute configuration of the terminal thiazoline ring, as well as the oxidized nature of the internal oxazole ring (Figure 1). A similar result was

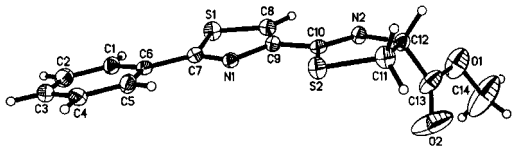
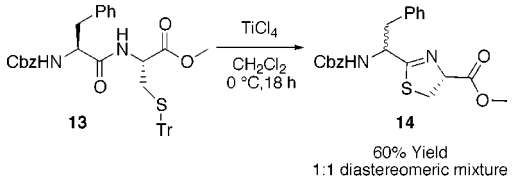


Figure 1. X-ray crystal structure of bis-heterocycle **12**.

observed by Charette et al. in their synthesis of bis-thiazolines using a different strategy.[4j] Apparently, contiguous thiazoline rings with H at the C(4) position are susceptible to rapid oxidation.[8]

To probe racemization at the C(2)-exomethine carbon and to possibly gain insight into the selective oxidation observed in the synthesis of **12**, fully protected dipeptide **13** was synthesized.[9] Deprotection−cyclodehydration of compound **13** using $TiCl_4$ afforded a 1:1 mixture of the corresponding diastereomeric thiazolines (60% yield) (Scheme 4). Race-

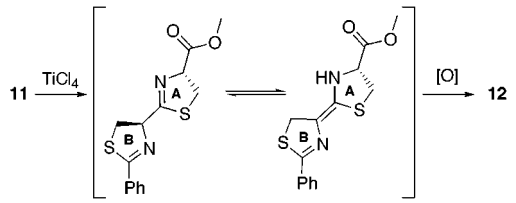
Scheme 4



mization of the C(2)-exomethine chiral center limits the utility of this approach for the formation of thiazolines within peptides.

In the selective oxidation of a thiazoline ring associated with the $TiCl_4$-mediated synthesis of **12**, it is reasonable to assume that the bis-thiazoline intermediate readily tautomerizes, which may predispose thiazoline ring B to oxidation (Scheme 5).

Scheme 5



In conclusion, the $TiCl_4$-mediated tandem deprotection−cyclodehydration of simple trityl-protected cysteine *N*-amide derivatives is a versatile procedure for the synthesis of thiazolines in moderate to high yields with generally good

stereoselectivities. This method is also useful for conversion of protected Cys-Cys dipeptides into linearly fused thiazole−thiazoline heterocycles (e.g., **11** → **12**). The most significant limitation identified is racemization at the C(2)-exomethine position associated with the $TiCl_4$-mediated synthesis of thiazolines within peptides.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **1**−**12** and an X-ray structure report for **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Air oxidation of thiazoline rings in tantazole A, tantazole I, and mirabazole A during their isolation and purification has been reported to afford thiazoles (see: refs 1a and 1b).

(9) Compound **13** was synthesized in solution by standard protocols using HOBT (1.1 equiv), HBTU (1.1 equiv), and DIEA (2.1 equiv) in DMF to mediate amide bond formation.