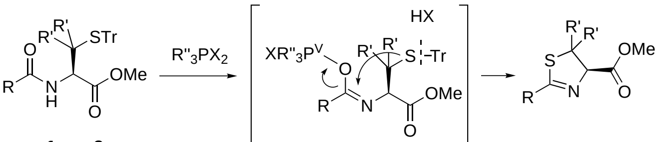
Biomimetic Heterocycle Synthesis

A Biomimetic Synthesis of Thiazolines Using Hexaphenyloxodiphosphonium Trifluoromethanesulfonate**

*Shu-Li You, Hossein Razavi, and Jeffery W. Kelly**

Thiazoline heterocycles are found in many bioactive natural products of peptide origin.[1] This substructure confers conformational rigidity and serves as a recognition site for DNA, RNA, and protein binding. Thiazolines are biosynthesized from peptides by nucleophilic attack of the cysteine thiol group on the amide carbonyl group of the preceding residue, followed by dehydration.[2] Although the biosynthesis of thiazolines employs cysteine residues, most chemical syntheses use serine residues, whereby the side chain is transformed into an electrophile that is attacked by the thioamide group of the preceding residue.[3] Here we report a facile and efficient biomimetic synthesis of thiazolines by treating N-acylated cysteine substrates with hexaphenyloxodiphosphonium trifluoromethanesulfonate to activate the amide group. The reaction proceeds in high yield with retention of configuration at the C4- and C2-exomethine carbon atoms of the thiazoline. Previous reports describe the scope and limitations of a mechanistically similar transformation with a Ti^{IV} reagent.[4]

Dehydrocyclization of a fully protected *N*-acyl cysteine residue requires activation of the amide bond, as well as deprotection of the side chain. We envisioned that the oxophilicity and Lewis acidity of phosphonium salts or phosphoranes should enable them to perform both transformations simultaneously (Scheme 1). To test this hypothesis, a number of commercially available or easily prepared phosphonium salts and phosphoranes were evaluated, a few of which are outlined in Table 1. We discovered that phosphorus reagent **C**, derived from triphenylphosphane oxide and triflic anhydride, converted fully protected cysteine **1a** (Scheme 1; R = Ph, R′ = H) to the corresponding thiazoline **1b** (Table 1, entry 3). Interestingly, phosphorus reagents **A** and **B** did not react with **1a** (Table 1, entries 1 and 2).



1a – 6a **1b – 6b**

Scheme 1. Proposed mechanism for the synthesis of thiazolines with a P^V reagent.

Although reagent **C** is known to activate and dehydrate amide carbonyl groups to afford nitriles, likely through a oxo-bridged diphosphonium salt,[5–6] its structure has never been conclusively determined.[7] Hence, this water-sensitive phosphorus reagent was crystallized, and X-ray diffraction revealed an O-bridged bis-phosphonium salt (Figure 1).

To ensure that the solid-state structure is relevant to the reactive species in solution, the ^{31}P NMR spectrum of the crystallized reagent was compared to those of reagents

Table 1: Synthesis of thiazoline **1b** from **1a** under a variety of reaction conditions.[a]

Entry	Reagent[b]	Solvent	*t*	Yield [%][c]	*ee* [%][d]
1	**A**	CH_2Cl_2	48 h	–	–
2	**B**	CH_2Cl_2	48 h	–	–
3	**C**	CH_2Cl_2	10 min	98	> 99.5
4[e]	**C**	Et_2O	48 h	98	> 99.5
5	**C**	THF	48 h	75	> 99.5
6	**C**	CH_3CN	10 min	96	> 99.5

[a] Reactions were carried out at 0 °C unless otherwise indicated. [b] **A**: hexamethylphosphoramide (3.0 equiv)/Tf_2O (1.5 equiv); **B**: Ph_3PBr_2 (1.5 equiv); **C**: Ph_3PO (3.0 equiv)/Tf_2O (1.5 equiv). [c] Yield of isolated product based on **1a**. Treating **1a** with triflic anhydride alone affords 55 % yield of **1b**. [d] Determined by HPLC on a Chiralcel OD column. [e] Reaction at 25 °C.

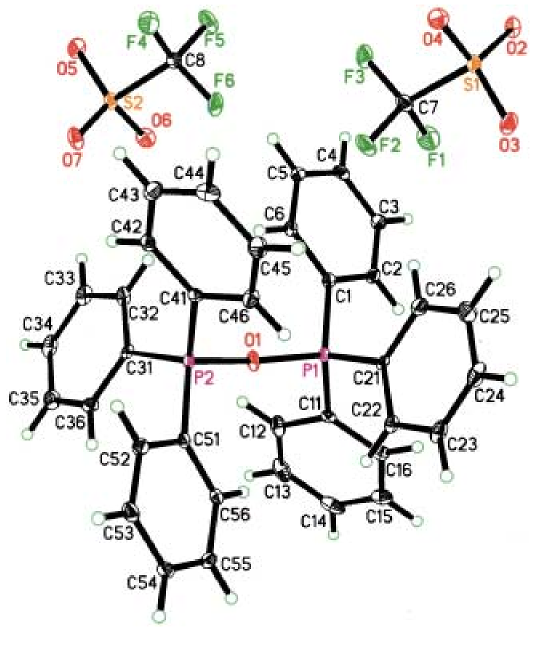


Figure 1. X-ray crystal structure of phosphorus reagent **C**. CCDC-192890 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+ 44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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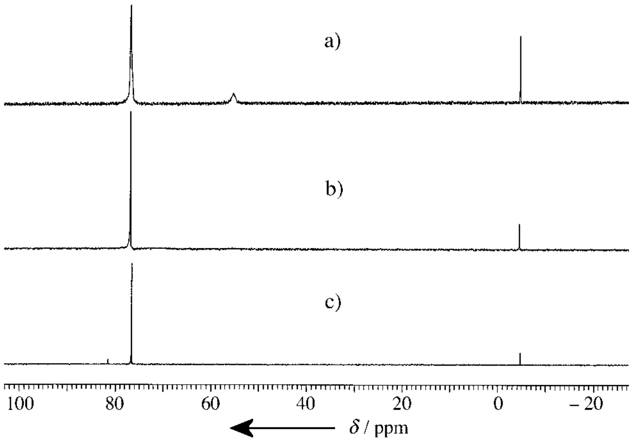


Figure 2. ^{31}P NMR spectra of crystallized **C**, and of **C** prepared in solution. All spectra were recorded in CD_3CN at 400 MHz (Ph_3P as the internal standard in a microtube, $\delta = -4.7$ ppm). a) Crystallized reagent **C**; b) Ph_3PO (2 equiv) and Tf_2O (1 equiv); c) Ph_3PO (1 equiv) and Tf_2O (1 equiv).

generated with different reaction stoichiometries of triphenylphosphane oxide and triflic anhydride (Figure 2). This study showed that reagent **C**, characterized crystallographically (Figure 1), is the sole species in solution, irrespective of whether one or two equivalents of triflic anhydride are used with two equivalents of triphenylphosphane oxide.

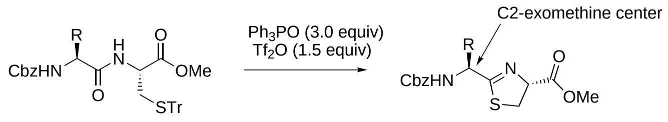
To examine the scope and limitations of this reaction, a few fully protected cysteine *N*-amide derivatives were synthesized and subjected to the optimized reaction conditions (Table 2). In general, these reactions afforded optically pure products in moderate to high yields, without any appreciable substituent effects on stereoselectivity. Lower optical purity was observed only with the *p*-NO_2-substituted substrate with extended reaction time (over 15 min). It is feasible to utilize a catalytic amount of triphenylphosphane oxide in the preparation of thiazoline **1b** without a significant decrease in yield or stereoselectivity (Table 2, entry 6).

To apply this mild method to the synthesis of thiazolines from peptides, four Cbz-protected dipeptides were synthesized (**7a**–**10a**, see Table 3). Thiazolines derived from these dipeptides are of particular interest, since these motifs are routinely found in bioactive marine metabolites.[2,8] In all cases, thiazolines were synthesized in high yields and with minimal loss of stereochemical integrity at the C2-exomethine centers.

To demonstrate the utility of this method in one-pot tandem cyclodehydrations, the fully protected Cys–Cys dipeptide **11a** was synthesized.[9] The reaction of this substrate was sluggish at 0 °C. However, it proceeded smoothly at ambient temperature to give the corresponding thiazole–thiazoline product **11b** in very high chemical yield and optical purity (Scheme 2). Rapid selective oxidation of bis-thiazolines to thiazole–thiazoline products was previously established.[1a,b,10]

In conclusion, the O-bridged bistriphenylphosphonium salt **C** promotes deprotection and dehydrocyclization of simple cysteine *N*-amides to give the corresponding thiazolines in excellent chemical and optical yields. This mild method was extended to the synthesis of thiazolines from

Table 3: Synthesis of thiazolines from cysteine-containing dipeptides.[a]



7a–10a **7b–10b**

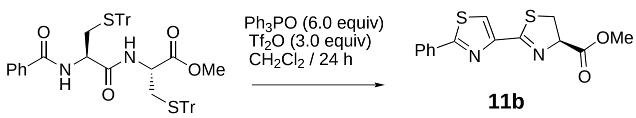
R	T [°C]	t [min]	Starting material (d.r.)	Yield [%][b]	Product (d.r.)[d]	*ee* [%][d]
Bn	0	10	**7a** (>99:1)	84	**7b** (93:7)[c]	>99.5
Bn	−20	120	**7a** (>99:1)	98	**7b** (97:3)[c]	>99.5
Me	−20	120	**8a** (99:1)	84	**8b** (91:9)	>99.5
*i*Pr	−20	120	**9a** (98:2)	86	**9b** (97:3)	>99.5
*s*Bu	−20	120	**10a** (96:4)	95	**10b** (96:4)	>99.5

[a] Reactions with 3 equiv Ph_3PO and 1.5 equiv Tf_2O in dichloromethane. [b] Yields of isolated products. Treatment of the protected dipeptide **7a** with triflic anhydride alone yields a very complex reaction mixture. [c] Diastereomeric ratio of the crude reaction mixture was determined by NMR spectroscopy at 500 MHz. [d] Diastereomeric ratio was determined by HPLC on a Chiralcel OD or OD-H column; *ee* is that of the major product.

Table 2: Synthesis of thiazolines from simple cysteine derivatives under optimized conditions.[a]

Entry	Substrate (config.)	R	R′	Product (Yield [%])[b]	*ee* [%][c]
1	**2a** (D)	Ph	H	**2b** (98)	>99.5
2	**3a** (L)	Ph	Me	**3b** (98)	99
3	**4a** (L)	4-$MeOC_6H_4$	H	**4b** (92)	>99.5
4[d]	**5a** (L)	4-$NO_2C_6H_4$	H	**5b** (86)	>99.5
5	**6a** (L)	$PhCH_2CH_2$	H	**6b** (84)	>99.5
6[e]	**1a** (L)	Ph	H	**1b** (96)	>99.5

[a] Reactions were carried out with 3 equiv Ph_3PO and 1.5 equiv Tf_2O in dichloromethane at 0 °C for 10 min. [b] Yield of isolated product based on the cysteine substrate. [c] Determined by HPLC on a Chiralcel OD column. [d] The reaction was quenched after 5 min. [e] Reaction with 0.1 equiv Ph_3PO and 1.5 equiv Tf_2O in dichloromethane at 0 °C for 60 min.



11a **11b**

63% yield, > 99.5% *ee*

Scheme 2. Synthesis of a thiazole–thiazoline bisheterocycle from a fully protected Cys–Cys dipeptide.

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cysteine-containing dipeptides in high yield and without significant loss of chirality at the C2-exomethine carbon atom. Finally, the application of this method to one-pot tandem dehydrocyclizations afforded a thiazole–thiazoline product in good overall yield and with excellent stereocontrol.

Experimental Section

General procedure for synthesis of thiazolines: Trifluoromethanesulfonic anhydride (50 μL, 0.3 mmol) was added slowly to a solution of triphenylphosphane oxide (167 mg, 0.6 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C. The reaction mixture was stirred for 10 min at 0 °C and then adjusted to the desired reaction temperature, followed by addition of the fully protected cysteine *N*-amide (0.2 mmol). The reaction progress was monitored by TLC. The reaction mixture was quenched with 10% aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The resultant crude product was purified by flash chromatography with EtOAc/hexanes. More details and characterization data of the products can be found in the Supporting Information.

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[9] Compounds were synthesized in solution by standard protocols using 1-hydroxybenzotriazole (HOBT, 1.1 equiv), 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU, 1.1 equiv), and diisopropylethylamine (DIEA, 2.1 equiv) in DMF to mediate amide bond formation.

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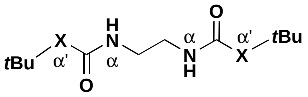
H-Bond-Supported Oxo Bridges

Hydrogen Bonds around $M(\mu\text{-}O)_2M$ Rhombs: Stabilizing a $\{Co^{III}(\mu\text{-}O)_2Co^{III}\}$ Complex at Room Temperature**

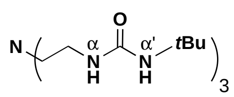
*Peter L. Larsen, Terry J. Parolin, Douglas R. Powell, Michael P. Hendrich, and A. S. Borovik**

Species with $\{M(\mu\text{-}O)_2M\}$ rhombs containing late 3d transition metal ions are proposed as key intermediates in biological and chemical processes.[1–4] Studies on metalloenzymes suggest that noncovalent interactions between the protein-derived active-site structures and the $\{M(\mu\text{-}O)_2M\}$ cores are often necessary for function.[1b,5] These types of interactions, such as hydrogen bonds (H-bonds), are often difficult to replicate in synthetic systems,[6] which may partially explain the thermal instability of many complexes containing $\{M(\mu\text{-}O)_2M\}$ cores: reported examples that contain Co^{III}, Ni^{III}, and Cu^{III} ions are only stable at temperatures below −20 °C. Herein we describe the preparation and characterization of $[Co^{III}H_2\mathbf{1}(\mu\text{-}O)]_2^{2-}$, which is stable at room temperature, in part, because of intramolecular H-bonds that form with the bridging oxo ligands of the $\{Co^{III}(\mu\text{-}O)_2Co^{III}\}$ core. These results add to the growing body of evidence that demonstrates the importance of noncovalent interactions in regulating the properties of metal–oxo complexes.



$H_4\mathbf{1}$ X = NH

$H_2\mathbf{2}$ X = O



$H_6\mathbf{3}$

We have recently shown that monomeric Fe^{III} and Mn^{III} complexes with a terminal oxo or hydroxo ligand can be isolated by confining the $\{M^{III}\text{–}O(H)\}$ units within rigid H-bond cavities.[7] These complexes were prepared with the

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