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Organolithium-Mediated Diversification of Peptide Thiazoles

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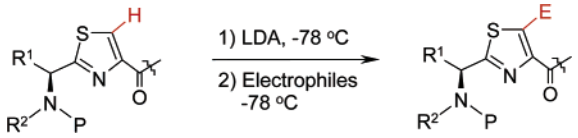
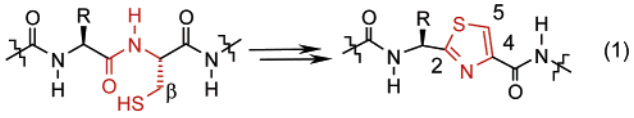
ABSTRACT



We report a one-step, racemization-free method for the diversification of peptide thiazoles via direct lithiation of the thiazole ring. The method is compatible with *N*-Boc, *N*-trityl, carboxylic ester, and carboxamide protecting groups and has been used to directly functionalize the thiazole ring of cyclopeptide natural products.

Peptide thiazoles are common substructures of macrocyclic natural products[1] that exhibit a range of biological activities, including potent immunosuppression,[2] inhibition of bacterial protein synthesis,[3] and actin filament stabilization.[4] In addition, macrocyclic peptides containing thiazoles have been synthesized with the aim of creating conformationally preorganized scaffolds, which can potentially interact with large protein surfaces and thus disrupt protein−protein interactions.[5]

The common biosynthetic precursor of peptide thiazoles is cysteine, the β-carbon of which becomes C5 of the thiazole heterocycle (eq 1).[1a] Perhaps because of this biosynthetic



(1)

constraint, the majority of peptide thiazole natural products lack C5 substituents.[6] To increase the structural diversity of macrocyclic peptide thiazoles, we sought a method that would allow facile substitution at C5 of the thiazole ring. Existing methods for the synthesis of 5-substituted dipeptide thiazoles require 4−7 steps *after* incorporation of the C5 substituent.[7] A more efficient route would place the C5 diversification step as late as possible, using fully assembled peptide thiazoles.

We considered that direct lithiation of peptide thiazoles would provide an efficient C5 diversification strategy. Although C5 lithiation of 2,4-disubstituted thiazoles is precedented,[8] lithiation of peptide thiazoles has not been reported previously. Here, we report the direct lithiation of

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(3) (a) Rodnina, M. V.; Savelsbergh, A.; Matassova, N. B.; Katunin, V. I.; Semenkov, Y. P.; Wintermeyer, W. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 9586. (b) Cameron, D. M.; Thompson, J.; March, P. E.; Dahlberg, A. E. *J. Mol. Biol.* **2002**, *319*, 27.

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(6) For examples of peptide thiazole natural products with 5-methyl and 5-methoxymethyl substituents, see: (a) Selva, E.; Beretta, G.; Montanini, N.; Saddler, G. S.; Gastaldo, L.; Ferrari, P.; Lorenzetti, R.; Landini, P.; Ripamonti, F.; Goldstein, B. P. *J. Antibiot.* **1991**, *44*, 693. (b) Shimanaka, K.; Kinoshita, N.; Iinuma, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1994**, *47*, 668.

(7) (a) Gordon, T. D.; Singh, J.; Hansen, P. E.; Morgan, B. A. *Tetrahedron Lett.* **1993**, *34*, 1901. (b) Buchanan, J. L.; Mani, U. N.; Plake, H. R.; Holt, D. A. *Tetrahedron Lett.* **1999**, *40*, 3985. (c) Suzuki, T.; Nagasaki, A.; Okumura, K.; Shin, C.-G. *Heterocycles* **2001**, *55*, 835. (d) Nagasaki, A.; Adachi, Y.; Yonezawa, Y.; Shin, C.-G. *Heterocycles* **2003**, *60*, 321.

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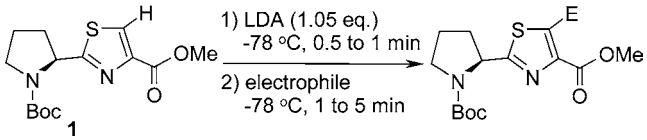
thiazole-containing peptides, including the cyclopeptide natural products ceratospongamide and epiceratospongamide.[9] The resulting 5-lithiated thiazoles react rapidly with a variety of electrophiles to provide substitution products in high yields and without epimerization.

We optimized lithiation conditions using a thiazole dipeptide derived from L-proline, Boc-L-Pro-Thia-OMe (**1**) (Thia = thiazole), an intermediate used in the total synthesis of ceratospongamide.[10] Treatment of **1** with 1.05 equiv of LDA for 30 s at −78 °C, followed by reaction with iodine for 5 min, provided the desired 5-iodo adduct in 87% yield (Table 1, entry 1). The methyl ester and Boc groups were stable under these conditions.[11] Importantly, there was no racemization at the proline-derived chiral center, as determined by a modified Marfey protocol (see Supporting Information).[12]

Table 1. Diversification at Thiazole C5 in Boc-L-Pro-Thia-OMe **1**



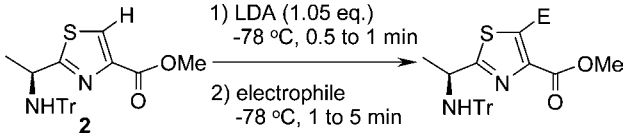
entry	electrophile	product E =	yield (%)[a]
1	I_2	I	87
2	Br_2	Br	80
3	TsCl	Cl	82
4	Bu_3SnCl	$SnBu_3$	97
5	BnS-SBn	SBn	72
6	BocN=NBoc	NBocNHBoc	43[b]
7	EtOCOCl	COOEt	77
8	PhCOCl	COPh	70
9	DMF	CHO	68
10	PhCHO	CH(OH)Ph	88[c]
11	acetone	$C(OH)Me_2$	81
12	Me-I	Me	68
13	$BrCH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	85[d]

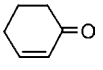
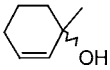
[a] Isolated yield. [b] ~20% of 5-^{t}BuO_2C-thiazole formed. [c] 1:1 diastereomer ratio at C5 α position. [d] 0.1 equiv of CuCN·2LiCl$_2$ used.

Encouraged by this result, we explored the scope of this reaction with various electrophiles (Table 1). Reaction of lithiated **1** with bromine and tosyl chloride[13] provided the 5-bromo and 5-chloro adducts, respectively, in excellent yields (entries 2 and 3). Reaction of lithiated **1** with tin, sulfur, and nitrogen-based electrophiles gave equally good results (entries 4−6). We next tested the reactivity of lithiated **1** toward a broad range of carbonyl electrophiles, including ethyl chloroformate, benzoyl chloride, DMF, benzaldehyde, and acetone. These reactions provided the corresponding ester, ketone, aldehyde, and alcohol adducts in good to excellent yields (entries 7−11). In the reaction with benzaldehyde, a 1:1 mixture of carbinol diastereomers was obtained. Alkylation of lithiated **1** succeeded with methyl iodide (entry 12) yet failed with allyl bromide (recovered starting material). This problem was solved by adding 0.1 equiv of CuCN·2LiCl$_2$;[14] the allylated product was thus obtained in 85% yield (entry 13).

To extend our method to dipeptide thiazoles containing amino acids other than proline, we focused on the L-alanine-based thiazole **2** (Table 2), available in 50% overall yield from *N*-trityl L-alanine (five steps, no purification of intermediates required). Despite the presence of a secondary amine, deprotonation with only 1.05 equiv of LDA,[11] followed by reaction with a variety of electrophiles, produced the 5-substituted adducts in 61−96% yields, again without

Table 2. Diversification at Thiazole C5 in Tr-L-Ala-Thia-OMe **2**



entry	electrophile	product E =	yield (%)[a]
1	I_2	I	73
2	TsCl	Cl	69
3	Bu_3SnCl	$SnBu_3$	67
4	BnS−SBn	SBn	96
5	BocN=NBoc	NBocNHBoc	61[b]
6	EtOCOCl	COOEt	65
7	PhCOCl	COPh	70
8	DMF	CHO	82
9	PhCHO	CH(OH)Ph	87[c]
10	acetone	$C(OH)Me_2$	72
11			82[c]
12	Me-I	Me	87
13	$BrCH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	80[d]
14	*n*-Bu-I	Bu-*n*	79[e]

[a] Isolated yield. [b] ~20% of 5-^{t}BuO_2C-thiazole formed. [c] 1:1 diastereomer ratio at C5 α position. [d] 0.1 equiv of CuCN·2LiCl$_2$ used. [e] 5 equiv of HMPA used. Tr = trityl.

(8) Metzger, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 6, pp 235−331.

(9) Tan, L. T.; Williamson, R. T.; Gerwick, W. H.; Watts, K. S.; McGough, K.; Jacobs, R. *J. Org. Chem.* **2000**, *65*, 419.

(10) (a) Yokokawa, F.; Sameshima, H.; Shioiri, T. *Synlett* **2001**, 986. (b) Deng, S.; Taunton, J. *J. Am. Chem. Soc.* **2002**, *124*, 916. (c) Kutsumura, N.; Sata, N. U.; Nishiyama, S. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 847. (d) Yokokawa, F.; Sameshima, H.; In, Y.; Minoura, K.; Ishida, T.; Shioiri, T. *Tetrahedron* **2002**, *58*, 8127.

(11) Lithiated thiazole **1** is stable at −78 °C for up to 30 min, with ~5% self-acylation product and ~10% other decomposition products; lithiated thiazole **2** is stable at −78 °C for at least 30 min with less than 2% self-acylation product. Both decompose rapidly at −40 °C.

(12) Fujii, K.; Ikai, Y.; Oka, H.; Suzuki, M.; Harada, K. *Anal. Chem.* **1997**, *69*, 5146.

(13) Brummond, K. M.; Gesenkerg, K. D. *Tetrahedron Lett.* **1999**, *40*, 2231.

(14) Abarbri, M.; Thibonnet, J.; Bérillon, L.; Dehmel, F.; Rottländer, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618.

racemization. In addition to the electrophiles shown in Table 1, we treated 5-lithiated **2** with cyclohexen-2-one, which gave the 1,2-adduct as a 1:1 mixture of diastereomers (entry 11). The 1,4-adduct was not detected. Although methylation and allylation proceeded uneventfully (entries 12 and 13), our initial attempts to alkylate **2** with 1-iodobutane failed. This problem was solved by the addition of 5 equiv of HMPA, which furnished the *n*-butyl adduct in 79% yield (entry 14). The 5-substituted dipeptide thiazoles shown in Tables 1 and 2 have orthogonally protected amines and carboxylic acids and are thus suitable for incorporation into linear and cyclic polypeptide structures.

Our interest in directly preparing 5-lithiated thiazoles in the context of polypeptides prompted us to test the model thiazole 4-carboxamide **3** (Figure 1). Lithiation of *N*-isopropyl carboxamide **3** with 1.05 equiv of LDA, followed by reaction with iodine for 5 min at −78 °C, provided only recovered starting material. However, the 5-iodo adduct **4** was obtained in 94% yield when 3.0 equiv of LDA was used.

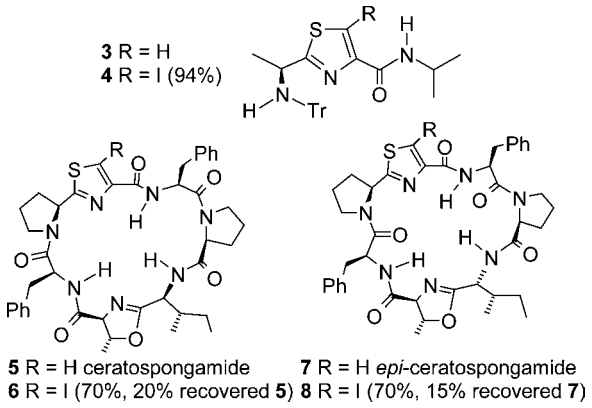


Figure 1.

To extend the thiazole lithiation chemistry to more complex systems, we turned to the cyclic peptide natural products ceratospongamide **5** and epiceratospongamide **7**.[11b,d] It should be noted that Shioiri and colleagues, in their correction of the originally proposed structure of **7**, found that the isoleucine α-stereocenter of **5** readily epimerized under acidic conditions to give **7**.[11d] Treatment of **5** or **7** with 4.2 equiv of LDA, followed by quenching with iodine, afforded the 5-iodo thiazole adducts in 70% yield. In both cases, we were unable to detect epimerization by HPLC or NMR analysis.

In summary, we have developed a one-step, epimerization-free method for appending diverse substituents to the 5-position of peptide thiazoles. The method is compatible with Boc and trityl protecting groups at the NH_2-terminus and ester and carboxamide groups at the CO_2H-terminus. We anticipate that the 5-bromo and iodo adducts will find application in Pd-catalyzed cross-coupling reactions, which will allow the preparation of diverse 5-aryl and heteroaryl peptide thiazoles. Thiazole lithiation occurred easily in the context of cyclopeptide natural products, thus providing access to structures that, to our knowledge, could not be obtained biosynthetically.

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

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