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Solid-Phase Synthesis of 1,3-Azole-Based Peptides and Peptidomimetics

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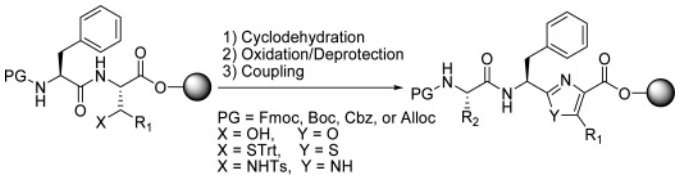
ABSTRACT



We report highly efficient two-step procedures for the synthesis of 1,3-oxazole-, thiazole-, and imidazole-containing peptides on solid phase from dipeptides composed of C-terminal threonine, serine, cysteine, or diaminopropionic acid by using different cyclodehydration procedures followed or preceded by oxidation. The methods are compatible with Fmoc solid-phase peptide synthesis conditions and with *N*-Fmoc, *N*-Boc, *N*-Cbz, and *N*-Alloc protecting groups.

A broad spectrum of natural products containing oxazoles and thiazoles has been isolated from marine organisms over the last two decades.[1] These compounds exhibit a wide range of biological activities, including cytotoxicity,[2] immunosuppression,[3] multiple drug resistance pump inhibition,[4] antibacterial, and antiviral activities.[5] Recently, there has been considerable interest in the use of these 1,3-azoles in macrocyclic peptides to create conformationally preorganized scaffolds.[6] In addition, 1,3-azole derivatives are useful synthetic intermediates and can be used as diversity scaffolds in combinatorial chemistry and also as peptidomimetics.[7] Because of their important role in bioactive compounds, combinatorial libraries, and peptidomimetics, we were interested in developing a convenient and highly efficient procedure to prepare oxazoles, thiazoles, and imidazoles directly on solid support from readily available amino acids. The main advantages of the solid-phase strategy are the use

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of more equivalents of reagents to ensure completion of the reaction, improved yields, purification as a final step, and suitability for combinatorial chemistry and Fmoc solid-phase peptide synthesis (Fmoc-SPPS).

Azole-based amino acids are usually prepared in solution and then used as building blocks in solution or solid-phase synthesis. Very few solid-phase syntheses of oxazoles and imidazoles have been reported.[8] Commonly used methods for the preparation of oxazoles, thiazoles, or imidazoles in solution include (1) a modified Hantzsch's procedure,[9] (2) a condensation reaction between N-protected imino ethers and serine esters, cysteine esters, or 2,3-diaminopropionic acid esters, respectively,[10] and (3) cyclodehydration of β-hydroxyamides or β-hydroxythioamides, respectively, using either Mitsunobu conditions or the Burgess reagent.[9b,11] The freshly synthesized 1,3-azolines are readily converted into 1,3-azoles by oxidation.[12] Alternative methods involve a Robinson−Gabriel cyclization of β-ketoamide or β-ketothioamide to obtain oxazoles and thiazoles, respectively.[13] Unfortunately, many of these methods are characterized by long synthetic sequences, harsh reaction conditions, or extensive purification leading to low overall yields. Our strategy to overcome this problem was to perform the heterocyclization directly on solid support from readily available amino acid derivatives.

Most naturally occurring oxazoles and thiazoles are formed by posttranslational modification of serine, threonine, and cysteine residues (Figure 1).[1c] Recently, You and Kelly reported a biomimetic synthesis of thiazolines and imidazolines from N-acylated cysteine or diaminopropionic acid substrates, respectively, using bis(triphenyl) oxodiphosphonium salts.[14] Herein, we report the utilization of biomimetic procedures on solid phase for the synthesis of oxazole-, thiazole-, and imidazole-containing peptides.

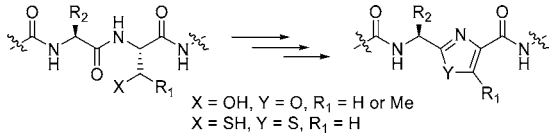

Figure 1. Biosynthesis of azole-containing peptides from serine, threonine, and cysteine residues.[1c]

Oxazole-based peptides can be synthesized from dipeptides composed of C-terminal threonine by oxidation of the side-chain followed by a mild Robinson−Gabriel cyclodehydration of the resulting β-ketoamide.[13] This very efficient method, reported by Wipf and Miller,[13] was chosen because of its compatibility with Fmoc-SPPS. To apply this method to solid-phase synthesis, N^{α}-protected dipeptides composed of phenylalanine and *O*-trityl-threonine were synthesized on Wang resin using standard Fmoc strategy.[15] After removing the trityl group with 1% TFA in CH_2Cl_2, the resin-bound dipeptides **1a**−**d** were subjected to oxidation using the Dess−Martin periodinane[16] to form the β-ketoamide derivatives **2a**−**d** (Table 1). Oxazole derivatives **3a**−**d** were obtained by cyclodehydration of the β-ketoamides **2a**−**d** using triphenylphosphine in the presence of iodine and diisopropylethylamine.[13] After cleavage from the resin with TFA, 5-methyloxazole-based dipeptides **4a**−**d** were obtained in good crude purity (67−78%) and in high yields (80−93% for six steps) based on the loading of the starting resin after HPLC purification (Table 1).[17]

β-Ketoamides **2a**−**d** were also transformed into thiazole-based dipeptides **5a**−**d** using the Lawesson's reagent[18] (Table 1).[6b] Cleavage from the resin with TFA afforded 5-methylthiazole-based dipeptides **6a**−**d** in good crude purity (70−89%) and in moderate yields (50−59% for six steps) after HPLC purification (Table 1).[17] The evaluated protecting groups were stable during the synthesis of **4a**−**d** and **6a**−**d**. The Boc group of **4c** and **6c** was removed during cleavage from the resin.

Another strategy to obtain oxazoles is to begin with the cyclodehydration using the Burgess reagent[19] followed by the oxidation step.[11a,b] This strategy applies particularly to the synthesis of oxazoles from serine residues because the previously described procedure was unsuccessful in this case. To apply this strategy to the solid phase, N^{α}-protected

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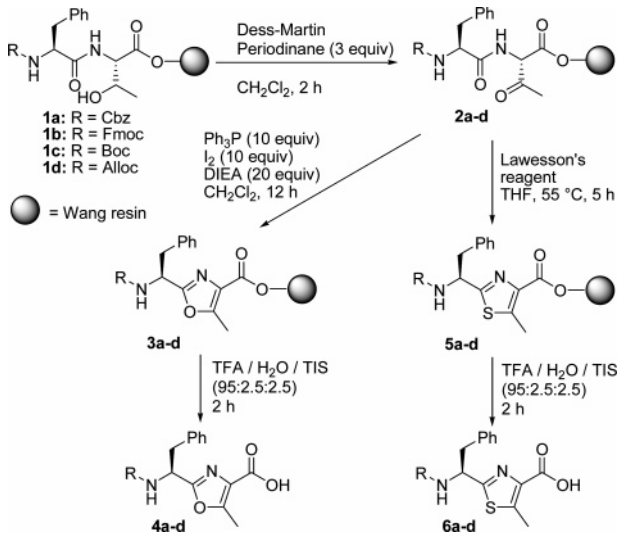
Table 1. Solid-Phase Synthesis of Oxazole- and Thiazole-Based Peptides from Threonine-Containing Dipeptides



entry	compound	R	purity (%)[a]	yield (%)[b]
1	**4a**	Cbz	78	89
2	**4b**	Fmoc	82	93
3	**4c**	H	67	80
4	**4d**	Alloc	71	88
5	**6a**	Cbz	89	52
6	**6b**	Fmoc	71	50
7	**6c**	H	70	55
8	**6d**	Alloc	76	59

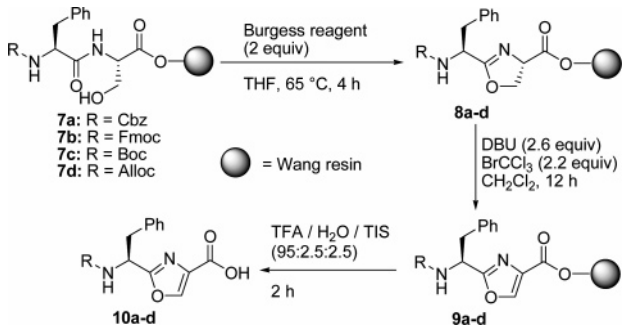
[a] Purity of crude products assessed using HPLC. [b] Isolated yield.[17]

dipeptides **7a**−**d**, composed of phenylalanine and serine, were synthesized on Wang resin following the same procedure as that for **1a**−**d**.[15] Cyclodehydration of resin-bound dipeptides **7a**−**d** was achieved with the Burgess reagent to yield the oxazoline derivatives **8a**−**d** (Table 2). Dipeptides **8a**−**d** were oxidized to oxazoles **9a**−**d** using $BrCCl_3$/DBU (1,8-diazabicyclo[5.4.0]undec-7-ene).[12c] After cleavage from the resin, oxazole-based dipeptides **10a**−**d** were obtained in good crude purity (72−90%) and in high yields (87−89% for six steps) after HPLC purification (Table 2).[17] The Fmoc protecting group of oxazoline-based dipeptide **8b** is removed during the oxidation step by the excess of DBU to yield the amine free oxazole-based dipeptide **9b**. The Boc group of **9c** was also removed during cleavage from the resin.

During cyclodehydration with the Burgess reagent, the nucleophilic attack is done by the amide or thioamide of the following residue on the activated β-hydroxyl group. Thiazoles can be obtained from cysteine by a different mechanism. In the biomimetic methodology reported by You and Kelly,[14e] the nucleophilic attack is done by the cysteine thiol of the preceding residue on the phosphonium-activated amide carbonyl group. Cyclodehydration is completed after dehydration via phosphine oxide formation. In this case, activation of the amide carbonyl is achieved by using bis(triphenyl) oxodiphosphonium trifluoromethanesulfonate.

To evaluate the compatibility of this methodology with Fmoc-SPPS, Cbz- and Fmoc-protected dipeptides **11a**,**b**

Table 2. Solid-Phase Synthesis of 1,3-Oxazole-Based Peptides from Serine-Containing Dipeptides

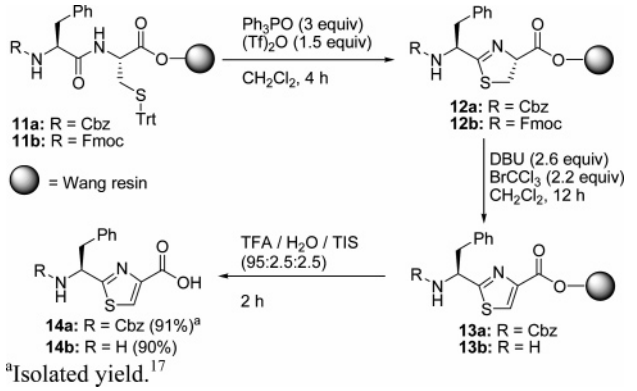


entry	compound	R	purity (%)[a]	yield (%)[b]
1	**10a**	Cbz	76	87
2	**10b**	H	90	89
3	**10c**	H	90	89
4	**10d**	Alloc	72	87

[a] Purity of crude products assessed using HPLC. [b] Isolated yield.[17]

composed of phenylalanine and *S*-trityl-cysteine were synthesized on Wang resin.[15] Dipeptides **11a**,**b** were transformed into thiazolines **12a**,**b** by a cyclodehydration−deprotection reaction using bis(triphenyl) oxodiphosphonium trifluoromethanesulfonate, generated from triphenylphosphine oxide and triflic anhydride (Scheme 1). Conversion of resin-

Scheme 1. Solid-Phase Synthesis of Thiazole-Based Peptides

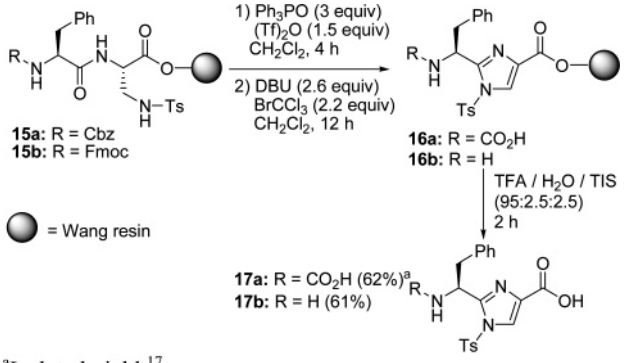


bound thiazolines **12a**,**b** to thiazoles **13a**,**b** was accomplished by oxidation with $BrCCl_3$/DBU.[12c] Thiazole-based dipeptides **14a** and **14b** were obtained in moderate crude purity (78% and 73%, respectively) after cleavage from the resin and in high yield (91% and 90% yield, respectively, for five steps) after HPLC purification (Scheme 1).[17] Fmoc deprotection is also observed during the oxidation step to yield the amine free thiazole-based dipeptide **13b**.

The oxodiphosphonium salt procedure can also be applied to prepare imidazole-based amino acid from dipeptides composed of C-terminal diaminopropionic acid.[14d] Cbz- and Fmoc-protected dipeptides **15a**,**b** composed of phenylalanine and β-tosylamino-α-aminopropionic acid were synthesized

on Wang resin. Conversion of **15a**,**b** to imidazole-based peptides **16a**,**b** was achieved by cyclodehydration with bis-(triphenyl) oxodiphosphonium trifluoromethanesulfonate followed by oxidation using $BrCCl_3$/DBU (Scheme 2). As

Scheme 2. Solid-Phase Synthesis of Imidazole-Based Peptides

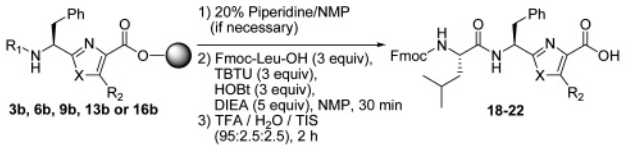


[a]Isolated yield.[17]

observed previously, the Fmoc protecting group was completely removed during the oxidation. However, removal of the benzyl group was also observed for **17a**. The generated carbamic acid was stable in acidic conditions and was observed by ^1H and ^{13}C NMR, MS, and HPLC. Imidazole-based dipeptides **17a** and **17b** were obtained in moderate crude purity (77% and 78%, respectively) after cleavage with TFA and in moderate yield (61% and 62% yield, respectively) after HPLC purification (Scheme 2).[17] Carbamic acids are unstable under basic conditions and can be easily removed by using a solution of 20% piperidine in NMP.

The suitability of the described procedures for Fmoc-SPPS was evaluated by coupling Fmoc-protected leucine to resin-bound azole-based dipeptides **3b**, **5b**, **9b**, **13b**, and **16b** using normal Fmoc-SPPS coupling conditions (Table 3).[15] Resin-bound dipeptides **3b**, **5b**, and **17b** were first treated with 20% piperidine in NMP to remove the remaining Fmoc protecting group (for **3b** and **5b**) or the remaining carbamic acid (**17b**). Surprisingly, the tosyl group of **17b** was completely removed during treatment with piperidine. Deprotection was not necessary for **9b** and **13b** because the Fmoc protecting group was removed during the oxidation step. Coupling of Fmoc-protected leucine on resin-bound amine free dipeptides **3b**, **5b**, **9b**, **13b**, and **16b** was achieved by TBTU/HOBt activation in the presence of DIEA. After cleavage from the resin, azole-containing tripeptides **18**−**22** were obtained in excellent crude purity (76−97%) and

Table 3. Synthesis of Azole-Containing Tripeptides



entry	Substrates, R_1	R_2	X	compd	purity (%)[a]	yield (%)[b]
1	**3b**, Fmoc	Me	O	**18**	91	87
2	**5b**, Fmoc	Me	S	**19**	82	52
3	**9b**, H	H	O	**20**	76	90
4	**13b**, H	H	S	**21**	87	88
5	**16b**, H	H	NH	**22**	97	64

[a]Purity of crude product assessed using HPLC. [b]Isolated yield.[17]

in moderate to good yields (52−90% for eight steps) after HPLC purification (Table 3).[17] Only one diastereoisomer was observed for compounds **18**−**22** as shown by HPLC of the crude products suggesting that the chiral integrity is conserved during the entire synthesis (eight steps).

In summary, easy and efficient solid-phase syntheses of oxazole-, thiazole-, and imidazole-based peptides have been achieved from readily available amino acids. The described procedures are compatible with Fmoc-SPPS and different commonly used protecting groups and provide a very efficient and flexible means to synthesize azole-based derivatives. Finally, the reported methodology allows the synthesis entirely on the solid phase of natural product libraries, small molecule combinatorial libraries, and peptidomimetics containing 1,3-azoles. In addition, we are currently investigating the synthesis of C5-substituted azoles and bisazoles using this methodology as well as the complete solid-phase synthesis of macrolactams and N1-substituted imdazole-based peptides and peptidomimetics.

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Supporting Information Available: Experimental details and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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