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Thiazole and oxazole building blocks for combinatorial synthesis

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Abstract

Three thiazole and oxazole containing amino acids were synthesized in good yields by condensation–cyclization. The active functional groups used, a *C*-terminal imino ester or a *C*-terminal aldehyde, reacted with both the amino groups and side chains of either serine or cysteine within 5 minutes at rt to form oxazolines or diasteriomeric mixtures of thiazolidines, respectively. The intermediate heterocyclic rings were then dehydrogenated to form the more stable, fully aromatic, rings. Ready availability of *N*-protected thiazole and oxazole-containing building blocks facilitates the solid-phase synthesis of natural products such as microcin B17 and other peptide-derived natural products that contain 2,4-linked thiazole and oxazole rings. © 1999 Elsevier Science Ltd. All rights reserved.

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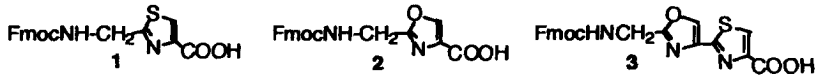
Thiazole and oxazole containing peptides obtained from microbial and marine origins exhibit important biological effects such as antitumor, antifungal, antibiotic and antiviral activities.[1–5] We investigated the synthesis of three *N*-protected thiazole and oxazole-containing amino acids **1**, **2**, and **3**.[6–8]



Our approach differs from the commonly used Hantzsch approach, because it relies on cyclizations of naturally occurring amino acid starting materials (Scheme 1) instead of the more difficult to prepare thioamides required for Hantzsch cyclization. Although cyclization gave the intermediate thiazolidines and oxazolines, dehydrogenation to generate the corresponding thiazoles or oxazoles was rarely straightforward.[9–14] Previously, the preparation of thiazole-containing peptides by cyclization of cysteine has been difficult,[9] because the acid-catalyzed cyclization of either cysteine or serine amino acid side chains within a peptide often resulted in cleavage of the amide bond, and many other side reactions.

The novel strategy we used to prepare the protected tripeptide (oxazolyl-thiazole) building block **3** is quite general. Scheme 1 details the preparation of useful, cyclic amino acid containing, synthons by

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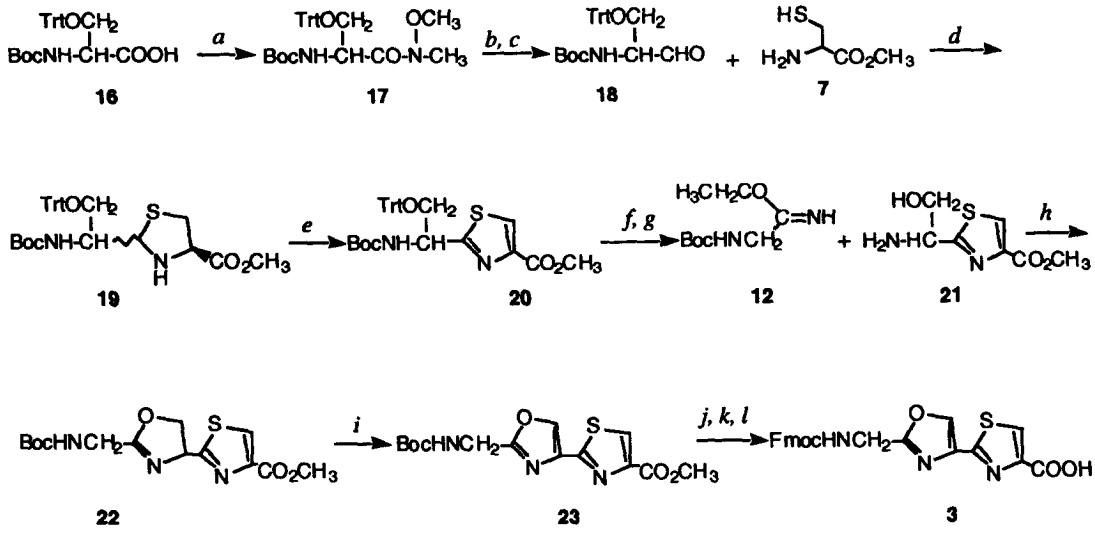

Scheme 1. (*a*) HCl·NHMe(OMe), BOP/DIEA/CH_2Cl_2, 20 min (98%); (*b*) LAH/ether, Ar, 0°C, 30 min; (*c*) 8% $KHSO_4$ (aq.) (b–c 94%); (*d*) DIEA/CH_2Cl_2/benzene evap. (3×) (95%); (*e*) active MnO_2, benzene–pyridine, 50°C, 5 h (59%); (*f*) TFA/TES/DCM (5:1:4), 45 min (90%); (*g*) HCl, rt; (*h*) CH_2Cl_2, rt, 24 h (g–h 44%); (*i*) NiO_2/benzene (1.6 equiv.), 70°C 10 h (22%); (*j*) NaOH/THF/H_2O, rt, 2 h (90%); (*k*) 40% TFA in CH_2Cl_2, 60 min; (*l*) Fmoc-OSu/THF/H_2O, 2 h (k–l 77%)

utilizing three amino acid starting materials, glycine, serine and cysteine, in a 'center-out' approach, wherein the peptide bond condensation and the ring cyclization steps occur simultaneously at room temperature in minutes.

To form thiazole rings, the same reaction sequence worked equally well, whether the rings were separated as in **1**, or directly attached to one another as in **3**. Thiazolidines were formed through condensation–cyclization by reaction of Boc-protected amino acid aldehydes with L-cysteine methyl ester **7**. The generation of the necessary amino acid aldehydes from the precursor imidate esters using LAH proceeded in excellent yields. Although THF was occasionally required, to dissolve some of the *N*-methoxy-*N*-methylamides, the yield was always improved by increasing the percentage of ether in the solvent mixtures (up to 100%). The key cyclocondensation was achieved by dropwise addition of **7** to a solution of the Boc-amino acid aldehyde in CH_2Cl_2 at rt. Unlike similar cyclocondensations reported in the literature,[11,15] the reaction was extremely rapid and did not require added $MgSO_4$, instantly affording a diastereomeric mixture of thiazolidines. Dehydrogenation of the thiazolidine mixture was performed with manganese(IV) oxide (activated) in benzene with pyridine to afford a single product thiazole (in compounds **1** and **3**).

To form the oxazole rings in compounds **2** and **3**, Boc-protected amino acid imino ethers reacted with L-serine **21** to form the intermediate oxazolines, which were then dehydrogenated to form the corresponding oxazoles. By substitution of triethyloxonium tetrafluoroborate for triethyloxonium hexafluorophosphate (which is more expensive) in the imino ether preparation step, and use of the $CuBr_2$/DBU/HMTA reagent[13] instead of the DBU/CCl_4/ acetonitrile/pyridine reagent[14] for the dehydrogenation of the oxazoline to form compound **2**, the yields were considerably improved. MnO_2 apparently oxidized the oxazoline to a more polar compound, instead of dehydrogenating it. Since the $CuBr_2$/DBU/HMTA reagent requires that the oxazolines have a 4-carbonyl group,[13] the more expensive nickel peroxide reagent was used to achieve dehydrogenation of oxazoline **22**. In all cases, the intermediate oxazolines were unstable, both in organic solvents and when dried in air; as has been previously reported[16] the oxazoline ring opens to form the corresponding dipeptide.

This condensation–cyclization approach to the synthesis of Boc- and Fmoc-protected cyclic amino acids has proven to be extremely versatile and general, and employs naturally-occurring amino acids to form the backbone of the building blocks. The direct formation of thiazolidines and oxazolines during the efficient room temperature condensation–cyclization step in our procedure eliminates many troublesome side reactions experienced with acid-catalyzed cyclizations. The condensation–cyclization step could also be used on the solid phase just as it was performed in solution. The general and efficient synthesis of protected thiazole and oxazole containing amino acids presented above, including the preparation of Fmoc oxazolyl-thiazole compound **3**, opens the way towards the preparation of a large number of diverse natural products using solid-phase synthesis.

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6. 2-(Fmoc-aminomethyl)-thiazole-4-carboxylic acid **1**: ^{1}H NMR (90 MHz, DMSO-d_6) δ ppm: 12.84 (s, br, 1H), 8.30 (s, 1H), 7.89–7.17 (m, 8H), 5.15 (s, br, 1H), 4.49–4.13 (m, 5H). ESI-MS (LC/MS, single quad, *m/z* 300–2200) $[M+H]^+$: 381.3, calcd monoisotopic mass: 381.09. TLC: R_f=0.44 ($CHCl_3$:MeOH:HOAc, 50:5:2). RPHPLC (C18, Vydac, 40–70% CH_3CN in 0.1% TFA over 30 min) 10.45 min.
7. 2-(Fmoc-aminomethyl)-oxazole-4-carboxylic acid **2**: ^{1}H NMR (90 MHz, MeOH-d_4) δ ppm: 8.37 (s, 1H), 7.77–7.17 (m, 8H), 4.42–4.09 (m, 5H). ESI-MS (*m/z*) $[M+H]^+$: 364.9, calcd monoisotopic mass: 365.11. TLC (as above): R_f=0.34. RPHPLC (as above) 10.93 min.
8. 2-(2′-Fmoc-aminomethyloxazole-4′-yl)-thiazole-4-carboxylic acid **3**: ^{1}H NMR (90 MHz, DMSO-d_6) δ ppm: 8.74 (s, 1H), 8.38 (s, 1H), 7.89–7.31 (m, 8H), 4.39–4.30 (m, 5H). ESI-MS (as above) $[M+H]^+$: 448.2, $[M+Na]^+$: 470.2, $[M+K]^+$: 486.2, calcd monoisotopic mass: 448.10. RPHPLC (as above): 14.18 min. Our solubility results conflict with those reported in Ref. 14. The white solid product was insoluble in CH_2Cl_2, ether, EtOAc, THF, methanol, ethanol, acetonitrile, HFIP, DMF, NMP, and water, but dissolved in DMSO. For use in peptide synthesis, it may be prepared as a 50% DMSO solution in either NMP of DMF.
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