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A METHOD FOR INTRODUCING SECONDARY AMIDE BONDS INTO STRAINED CYCLIC PEPTIDES

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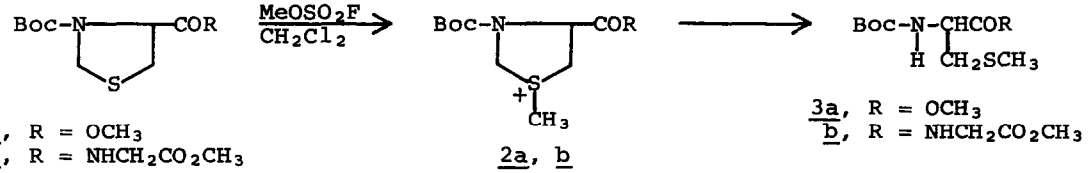
Conversion of small linear peptides into strained cyclic peptides is influenced by the configurational and amide bond sequence of the precursor. In some cases cyclization may be facilitated or prevented by placement of tertiary amide bonds ($-CONR_2$) in the linear sequence.[1,2] For example linear tripeptides can be cyclized only if all amide bonds are tertiary.[2] In order to synthesize cyclic tripeptides containing one or more secondary amide bonds (-CONHR) for chemical and conformational studies we have developed a method for converting the thiazolidine-4-carboxylic acid (Thz)[3] residue 1 into secondary, cysteinyl residues 3.

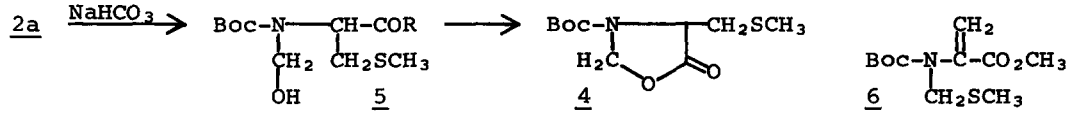


1a, R = OCH_3
b, R = $NHCH_2CO_2CH_3$

2a, b

3a, R = OCH_3
b, R = $NHCH_2CO_2CH_3$

Treatment of the methyl ester of Boc-Thz (1a) with methyl fluorosulfonate (purified by treatment with K_2CO_3 in methylene chloride and filtered) in methylene chloride at 0^0 under nitrogen gave the sulfonium salt 2a (100%). After decanting solvent, salt 2a was treated with saturated sodium bicarbonate for 5 min at 0^0 to give lactone 4:[4] (56%), NMR 1.46 (9H, s), 2.15 (3H, s), 3.06 (2H, m, AB portion of ABX; A, dd, J = 2.5, 15 Hz; B, 3.9, 16.95 Hz), 4.60 (1H, m, α-CH), 5.38 (2H, m), formed via the hydroxymethyl intermediate 5 (R = OCH_3). Treatment of sulfonium salt 2a under anhydrous conditions (triethylamine in methylene chloride)[5] gave the unsaturated methylthiomethyl derivative 6.[4]



Lactonization does not occur when the ester group is replaced by an amide

group. Treatment of Boc-Thz-Gly-OMe (2b) with methyl fluorosulfonate followed by sodium bicarbonate as described above gave the dipeptide, Boc-Cys(Me)-Gly-OMe (3b): (74% yield)[4], NMR ($CDCl_3$) 1.4 (9H, s), 2.15 (3H, s), 2.84 (2H, m), 3.70 (3H, s), 4.09 (2H, d), 4.28 (1H, m), 8.36 (NH, t), 8.10 (NH, d, J = 7 Hz).

Opening the Thz residue provides a route to cyclic peptides containing one secondary amide bond more than found in the sequence used for cyclization. For example, Boc-L-MeAla-L-Leu-L-Thz-GlyOMe (7) was prepared by solid phase synthesis[6], and converted to the free amine-trichlorophenyl ester derivative (8). Cyclization at 90° in pyridine gave the cyclic tetrapeptide 9 (two secondary amide bonds): (11% yield)[4]; mass spectrum, M^+ 370 (0.69%), 309, 285, 212, 197, 169, 141, 113, 84, 70, 71. Treatment of peptide 9 with methyl fluorosulfonate followed by sodium bicarbonate gave the cyclic tetrapeptide 10,[4] (three secondary amide bonds) in 61% yield: mass spectrum m/e M^+ 372 (0.5%), 325, 310, 282, 212, 197, 169, 141, 114, 86, 58. The NMR shows signals for the S-Me group at 2.15 ppm and one additional NH signal at 7.46 ppm.

cyclo(L-MeAla-L-Leu-L-Thz-Gly) ⟶ cyclo(L-MeAla-L-Leu-L-Cys(Me)-Gly-)

9 10

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3. IUPAC-IUB Recommended abbreviations for amino acids and peptides, J. Biol. Chem., 247, 977(1972); Cys(Me) = S-methylcysteine.
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