Synthesis of Cyclic Acylated Enamino Ester Dipeptide Analogues via the Bromolactonization of a Keto Acid Phosphorane

Andrew D. Abell* and Jane M. Taylor

Department of Chemistry, University of Canterbury, Christchurch, New Zealand

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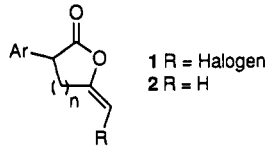
Summary: The acylated cyclic enamino ester dipeptide analogues **12**, **13**, and **17–19** have been prepared via lactonization of the keto acid phosphorane **8** followed by incorporation of an amino acid into the product enol lactones **9**, **10**, and **16**.

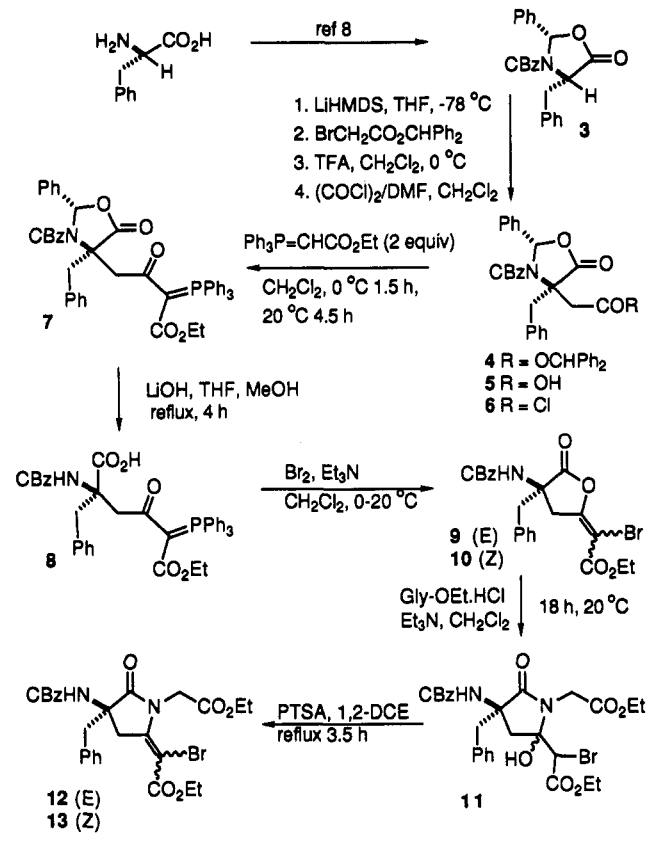
Serine proteases have been implicated in a number of pathological conditions, for example, emphysema, tumour invasion, and arthritis.[1] Specific inhibitors of these proteases are useful therapeutic agents. Haloenol lactones of the type **1** are mechanism-based inhibitors of serine proteases,[2] and hydrogen enol lactones of the type **2** are alternate substrate inhibitors of α-chymotrypsin.[3] Ha-



1 R = Halogen
2 R = H

loenol lactones function as irreversible inhibitors by releasing an electrophilic α-halo ketone on protease action.[2] Simple lactams have also been used as conformationally constrained amino acid analogues to enhance inhibitor potency.[4] Enzyme–substrate recognition, although primarily dependent on the interaction between the enzyme primary specificity pocket and the cleavage amino acid of the substrate, is also dependent on secondary interactions. The aim of the present study is to take a serine protease peptide recognition sequence and incorporate a known latent reactive entity (as in compounds **12** and **13**) or an alternate substrate entity (as in compounds **17–19** and **21**) to increase inhibitor selectivity and potency.[5] The synthesis of these compounds utilizes a new, versatile, and high-yielding bromo lactonization reaction[6] (modified α-substitution plus carbonyl olefination via β-oxido phosphorus ylides reaction or SCOOPY reaction[7]) of a keto acid phosphorane, e.g., **8**, to yield a bromo enol lactone, e.g., **9** and **10**. Lactonization of **8** in the absence of Br_2 gave the corresponding hydrogen enol lactone **16**. The introduction of an amino acid into the enol lactones gave the peptide analogues **12**, **13**, **17–19**, and **21** via a general, mild, and high-yielding procedure.

Scheme I



The oxazolidinone **3**, devised by Seebach and coworkers[8], has been used extensively for the preparation of α,α-disubstituted amino acids (Scheme I). Treatment of **3** with lithium hexamethyldisilazide (LiHMDS), at −78 °C, generated the corresponding enolate which was alkylated with $BrCH_2CO_2CHPh_2$ to give **4** (95%) as a single isomer by ^1H and ^{13}C NMR spectroscopy. Removal of the benzhydryl ester with trifluoroacetic acid (TFA) gave the free acid, **5** (32%), which was treated with $(COCl)_2$ and DMF to give the corresponding acid chloride **6**. Reaction with 2 equiv of $Ph_3P{=}CHCO_2Et$ then gave the phosphorane **7** (95%) as a pair of conformational isomers by ^1H and ^{13}C NMR spectroscopy. The conformational isomerism is probably due to restricted rotation about the CBz group. The ^1H NMR spectrum of **7** in DMSO-d_6 at 80 °C indicated a single isomer. The key phosphorane **7** was also prepared (26%) by alkylation of the enolate generated from **3** with lithium hexamethyldisilazide, at −78 °C, with **14**.

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(8) For a review see: Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989.

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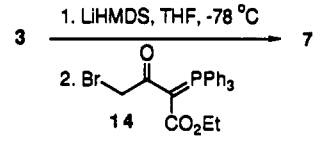
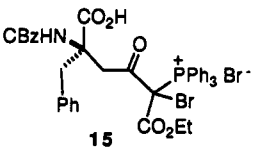


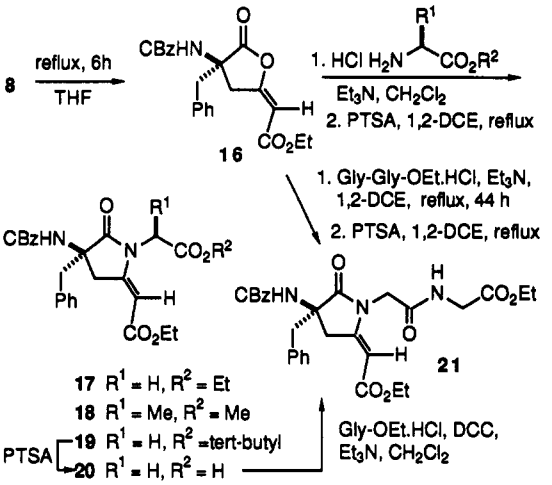
Selective hydrolysis of the oxazolidinone ring of **7** with LiOH in THF and MeOH gave the keto acid phosphorane **8** (95%). Bromolactonization with the loss of Ph_3PO was effected with Br_2 and Et_3N to give the bromo enol lactones **9** and **10** (1:1, 69%), which were separated by radial chromatography. The bromolactonization reaction represents a mild and general method for the preparation of bromo enol lactones from keto acid phosphoranes.[6] The reaction proceeds by initial formation of a bromo phosphonium salt, e.g., **15**, followed by lactonization, oxaphosphetane formation, and loss of Ph_3PO to give the enol lactone.[6]



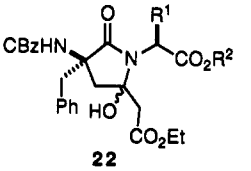
Treatment of either **9** or **10** in CH_2Cl_2 with Gly-OEt·HCl and Et_3N, at 20 °C, for 18 h, gave **11** (95%). Compound **11** was refluxed for 3.5 h in 1,2-dichloroethane (1,2-DCE), containing *p*-toluenesulfonic acid (PTSA), to give the *E* and *Z* acylated enamino esters **12** and **13**, respectively (65% combined yield). The reaction of an amine with readily available enol lactones[9] under the general conditions described above represents a convenient preparation of cyclic acylated enamino esters.[10] Traditional preparations of cyclic acylated enamino esters from an imide via either Wittig, Reformatsky, or Grignard chemistry suffer from very poor yields and harsh reaction conditions.[11]

The keto acid phosphorane **8** gave the *E* enol lactone **16** (73%) on refluxing in THF for 6 h. Reaction of **16** with the hydrochloride salts of Gly-OEt, Gly-O^{t}Bu, or Gly-Gly-OEt, and Et_3N gave an intermediate of the general type

Scheme II



22. Refluxing **22** in 1,2-dichloroethane, containing PTSA, gave the acylated enamino esters **17** (54% after chromatography), **19** (95%), and **21** (64% after chromatography). The *tert*-butyl ester of **19** was removed using PTSA to give **20**. Subsequent coupling with Gly-OEt·HCl using Et_3N and dicyclohexylcarbodiimide (DCC) gave the tripeptide analogue **21** (77%), with a ^1H NMR spectrum identical to the sample prepared by direct insertion of Gly-Gly-OEt into **16**. A similar reaction of **16** with L-Ala-OMe, followed by treatment with PTSA in refluxing 1,2-dichloroethane (Scheme II), gave **18** (78%) and <5% of another epimer by ^1H and ^{13}C NMR spectroscopy.



Studies on the protease inhibitory properties of the peptide analogues and the generality and reaction mechanism of the halo lactonization and amino acid insertion reactions are in progress.

Supplementary Material Available: Experimental procedures and key ^1H NMR spectra (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(10) Paper in preparation.
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