Notes

Solid-Phase Synthesis via 5-Oxazolidinones. Ring-Opening Reactions with Amines and Reaction Monitoring by Single-Bead FT-IR Microspectroscopy

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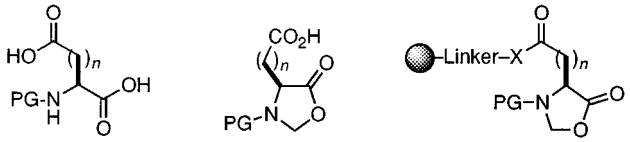
Introduction

Until recently, large compound libraries produced by solid-phase synthesis have been restricted to those of linear peptides and oligonucleotides, but the need for development and synthesis of libraries of small organic molecules using this method is growing rapidly.[1] We are interested in developing strategies and chemistries that would allow entry to combinatorial libraries of peptidomimetic structures on solid support. Our approach to the synthesis of peptide mimetics involves attachment of an essential amino acid residue via its side-chain functionality to the solid support. A similar strategy has been employed by Ellman in creating a peptidomimetic library using the hydroxyethylamino isostere of phenylalanine found in most HIV protease inhibitors anchored via the secondary alcohol.[2] Anchoring the amino acid side chain to polymeric supports is now widely used to prepare head-to-tail cyclic peptides via solid-phase-mediated cyclization.[3] Typically, Asp or Glu are attached via their ω-carboxyls to hydroxymethyl or aminomethyl resins, with the expectation that the corresponding peptides containing Asp/Glu or Asn/Gln, respectively, will be obtained after final cleavage from the resin. The most widely practiced strategy to obtain head-to-tail cyclic peptides uses the three-dimensional Fmoc/*t*-Bu/allyl orthogonal protection scheme. Kates *et al.* developed the use of α-allyl-protected aspartic acid for automated continuous flow synthesis of cyclic peptides containing Asp or Asn residues via side-chain anchoring to the resin followed by on-resin cyclization,[4] which is applicable to Glu- and Gln-containing sequences. Also, the Fmoc/allyl ester protection scheme was applied to anchor lysine via its ϵ-amino group.[3e] Additionally, side-chain attachment to Merrifield (chloromethylated polystyrene) resin has been applied to cysteine in its unprotected form; this has allowed both *N*- and *C*-terminal derivatization.[5] In the latter case, *C*-terminal derivatization to amides and esters required carboxylic acid activation with BOP reagent.

We present here an alternate protection scheme for side-chain anchoring to solid supports. Specifically, this paper demonstrates the utility of L-Asp- and L-Glu-derived *N*-substituted (oxycarbonyl)-5-oxazolidinones **1**−**3** as a selective means to protect the α-carboxylic acid prior to ω-carboxyl attachment to either hydroxymethyl or aminomethyl resin. Furthermore, we present the first



Aspartic Acid (n = 1)
Glutamic Acid (n = 2)

1-3
Oxazolidinones

4-7

solid-phase examples of oxazolidinone ring opening reactions using primary amines to provide the corresponding amides. The *N*-carbamate-protected amino acid 5-oxazolidinones have been previously used for functional group manipulation of the Asp and Glu side-chain residues,[6] and compounds **1** and **3** have been shown to undergo regioselective amidation at the α-carboxylic acid upon treatment with excess amine in solution.[7] One of the key advantages of employing oxazolidinones in solid-phase synthesis is their characteristic carbonyl IR absorption band at 1800 cm^{-1}. The lack of analytical tools for monitoring many solid-phase reactions is still a major problem in the production of combinatorial libraries.[8] Single-bead FT-IR microspectroscopy (single bead IR) has emerged as a powerful tool for real time monitoring of

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Table 1. Oxazolidinones 1-3 and Resin-Bound Oxazolidinones 4-7 Prepared and Used in This Study (See Experimental Details)

no.	n	PG	resin/linker−X	loading (mmol/g)
1	1	Cbz		
2	1	Alloc		
3	2	Alloc		
4	1	Cbz	AM-Knorr−NH	0.78
5	1	Alloc	AM-Knorr−NH	0.71
6	1	Alloc	Wang-O	0.64
7	2	Alloc	AM-Knorr−NH	0.92

solid-phase reactions.[9] In this work, we used single bead IR to facilitate method development, monitor reaction kinetics, and qualitatively estimate the oxazolidinone ring-opening reaction.

Results and Discussion

Starting from the *N*-carbamate-protected aspartic or glutamic acids, we first prepared in high yield (>90%) and purity (>95% by ^{1}H NMR) by known procedures[6a] (paraformaldehyde, *p*-TsOH, azeotropic removal of H_2O) the oxazolidinones **1**−**3**. Initially, we used the Cbz protecting group for the preparation of **1**, but switched to Alloc-protected oxazolidinones **2** and **3**, due to the facile removal of the Alloc group by Pd^0 under neutral conditions,[10] allowing further elaboration of the *N*-terminal on solid support. In the next step, the oxazolidinones **1**−**3** were attached to Knorr and Wang resin using standard DIC/HOAt or PyBrOP/HOAt coupling methods to provide **4** and **5**−**7**, respectively (see Table 1 and Experimental Section).[11] Percent nitrogen (determined by microanalysis) showed that the resin loading was quantitative, independent of the method used. Coupling to the Wang resin, which has been reported to be sometimes problematic,[3j] was found to be ca. 75% of theoretical. The polymer-bound oxazolidinones **4**−**7** were further analyzed by single "flattened" bead FT-IR microspectroscopy and compared to Fmoc-Knorr or Wang resin. They showed a characteristic strong carbonyl IR band at 1800 cm^{-1} that can be assigned to the carbonyl of the 5-oxazolidinone (Figure 1). This unique band serves as a useful and distinct indicator for product identification in reactions carried out on resins.[12]

Model studies were then performed to determine the reaction conditions for the ring opening of the polymer-bound oxazolidinones **4**−**7** with primary amines (Scheme 1). One of the major problems in solid-phase synthesis is the lack of a TLC-like flexible analytical tool for real-time analysis of the reaction.[1g] The single-bead IR method has the advantages of speed, nondestructive analysis, and small sample size.[9] This method was used to monitor the reaction of resin **4** with a 10-fold excess

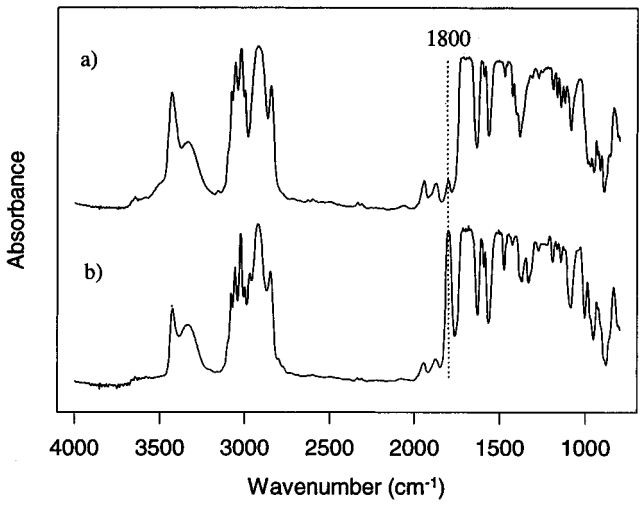
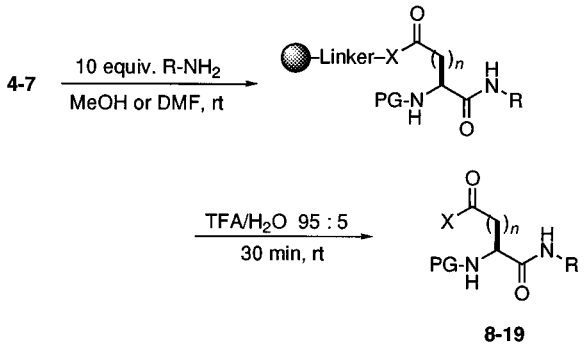


Figure 1. Single-bead FT-IR spectra taken from (a) Knorr−Fmoc resin, the starting material, and (b) after Fmoc-deprotection and coupling reaction with oxazolidinone **2**, which results in the formation of resin-bound oxazolidinone **5**. All spectra were taken using the transmission mode at room temperature as described in the Experimental Section. The band for the oxazolidinone carbonyl at 1800 cm^{-1} is indicated by the dotted line.

Scheme 1



of phenethylamine in methanol as solvent (ca. 0.8 mol/L solution). The time course of this reaction is shown in Figure 2. The intensity of the band at 1800 cm^{-1} decreased with time, indicating a rapid loss of starting oxazolidinone and formation of the resin-bound Asn amide. Integrations of the area under the oxazolidinone carbonyl band at 1800 cm^{-1} were analyzed, and the reaction time course appeared to be single exponential ($k = 1.23 \times 10^{-3}$ s^{-1}), suggesting that the reaction rate depended only on the available reactive sites on the resin when the other reagent was in excess. Several solid-phase reactions have exhibited pseudo-first-order reaction rates.[9c] Data analyzed by curve-fitting indicated clearly that the reaction was complete after 5 h. This was also confirmed by ^{1}H NMR evaluation of cleaved reaction material at specific time intervals throughout the reaction (data not shown). The lack of IR peaks associated with the potential hydrolysis ring-opened carboxylic acid side products (broad OH stretch 3300−2500 cm^{-1}) and the fit to a first-order reaction rate equation strongly suggest that there are no side reactions associated with oxazolidinone ring opening. This was further established by NMR analysis of the cleaved product (TFA/H_2O, 95:5). The Asn amide **8** was clearly identified and obtained in a crude mass yield of 80% in a purity of >90% as measured by percent area (% area) at 230 nM via RP-HPLC (Table 2).

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(12) The 5-oxo carbonyl band at 1800 cm^{-1} was distinctly observed on amino methyl resin when SCAL linker (Pátek, M.; Lebl, M. *Tetrahedron Lett.* **1991**, *32*, 3891−3894) was used (data not shown).

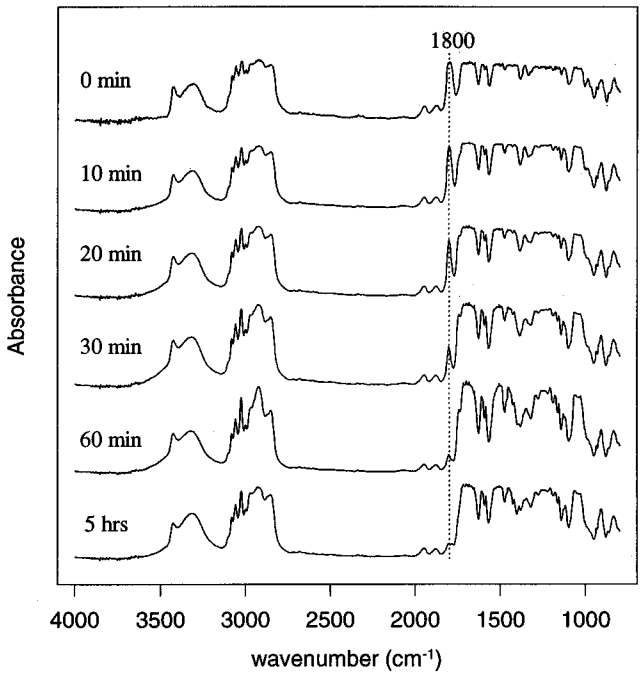


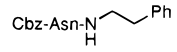
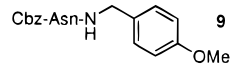
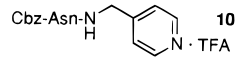
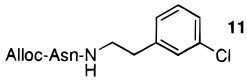
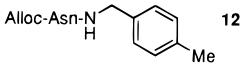
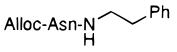
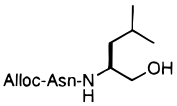
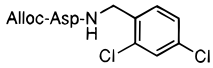
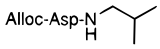
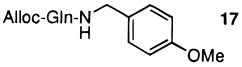
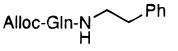
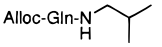
Figure 2. IR spectra taken from a single flattened bead at various times—0, 10, 20, 30, 60 min and 5 h—after initiation of the ring-opening reaction as depicted in Scheme 1 (samples were taken and washed with MeOH and THF and dried in vacuo). The decrease in the intensity of the 1800 cm^{-1} band was correlated with loss of oxazolidinone and the formation of the Asn amide.

We also examined effects of different solvents because swelling properties of polystyrene-based resins are more solvent dependent compared to PEG−PS-based resins.[13] For some amines we analyzed, we detected small amounts (<10%) of Asn methyl ester in the crude product when methanol was used. Tetrahydrofuran, methylene chloride, and DMF were also evaluated and found to be suitable solvents for the oxazolidinone ring-opening reaction with amines; therefore, we choose DMF (good polystyrene swelling properties) for our array synthesis.

Although the ring-opening reaction is usually complete within 5 h, the described parallel synthesis of 12 ring opening reactions was carried out overnight (ca. 15 h) to assure completion. Little or no side reactions were observed.

This basic work validated our approach and led to the synthesis of an array of different Asn, Asp, and Gln amides according to Scheme 1. Our method of oxazolidinone ring opening was not applied to side-chain-immobilized glutamic acid; however, we do not believe such reactions would be problematic. For this purpose, the resins were placed in a vial and swelled in DMF, and a 10-fold excess of the appropriate amine was added (ca. 0.8 mol/mL solutions in DMF). The mixtures were shaken overnight, and after washing (DMF, THF, and MeOH) and drying, the resin samples were analyzed by single "flattened" bead FT-IR microspectroscopy. For all entries listed in Table 2, we observed complete conversion, based on the absence of any absorption at 1800 cm^{-1}. Therefore, FT-IR on a single bead can be used as a "TLC-like" analytic method. After cleavage from the resin (TFA/H_2O, 95:5) and drying *in vacuo*, the crude products **8**−**19** were obtained in good yield (>80%) on the basis of the initial loading of the starting resins **4**−**7**. All new compounds were analyzed and characterized by RP-HPLC, mass spectroscopy, and ^1H and ^{13}C NMR spectroscopy. The purity of the crude materials **8**−**19**, as evaluated by RP-HPLC and NMR, is remarkably high (>80%). We are aware that percent purities extracted from HPLC chromatograms can not be absolutely derived from percent peak area without knowing absolute molar absorptivities for each product and impurities. However, for simplicity and practical matters, we used the HPLC data (% area) and NMR data (see Table 2 and Supporting Information) to demonstrate the high purity of the crude products **8**−**19**. NMR detected traces of solvent in many samples, but never any starting materials in the crude reaction products. For amide **14**, which used the α-branched amine, leucinol, we observed lower mass yield (ca. 40%) and lower purity (ca. 60% by RP-HPLC) compared to other amines investigated. On the basis of this initial observation, we also tested a second α-substituted amine, α-methylbenzylamine, and could only detect small amounts of the desired product (ca. 40% crude yield and ca. 50% purity, result not shown). When the reaction was tried with *N*-benzylphenethylamine, a secondary amine, no conversion was observed by single-

Table 2. Array Synthesis of Asn, Asp, and Gln Amides 8-19 *via* Ring-Opening Reaction of Polymer-Bound Oxazolidinones 4-7 with Amines

Starting Material	Product	No.	crude yield[a] (%)	RP-HPLC[b] % Area (t_R)
4		8	80	>95 (12.8 min)
4		9	> 95	>95 (12.1 min)
4		10	> 95	83 (7.9 min)
5		11	> 95	81 (12.4 min)
5		12	> 95	90 (9.6 min)
5		13	75	74 (8.9 min)
5		14	40	64 (14.3 min)
6		15	75	77 (14.6 min)
6		16	88	–[c]
7		17	> 95	91 (7.7 min)
7		18	> 95	95 (8.9 min)
7		19	> 95	–[c]

[a] Yields are calculated from the crude product mass based on the initial loading of the resins **4**−**7**. [b] Purity as % area determined by C18 RP-HPLC at 230 nm. [c] By ^1H NMR spectroscopy. Uniform product (>90%).

(13) Zalipsky, S.; Chang, J. L.; Albericio, F.; Barany, G. *React. Biopolym.* **1994**, *22*, 243−251.

bead FT-IR spectroscopy, even at higher temperature (80 °C). The same observation was made with anilines, *N*,*O*-dimethylhydroxylamine, and the free amine of an amino acid ester. Thus, it appears that the ring-opening reaction of polymer-bound oxazolidinones under these mild conditions (room temperature) is limited to aliphatic and benzylic primary amines as described for the solution reaction.[7]

In conclusion, we have demonstrated that the oxazolidinone protection scheme is suitable for side-chain immobilization of Asp and Glu and for "activation" of the α-carboxylic acid. The polymer-bound oxazolidinones underwent a ring-opening reaction with a wide range of primary aliphatic and benzylic amines to give in high yield and high purity Asn, Asp, and Gln amides. We further established single bead FT-IR microspectroscopy as an important and easy to use analytical tool in monitoring reactions on solid support. Especially, the oxazolidinone carbonyl IR band at 1800 cm^{-1} is a marker that enhances the utility of oxazolidinones as a α-carboxylic protection group on solid support. Additional studies on solid-phase organic synthesis *via* oxazolidinones are ongoing in order to explore other reactions and strategies to gain entry into the production of peptidomimetic structures.

Experimental Section

General Methods. Knorr resin (~0.8 mmol/g) was purchased from Advanced ChemTech and Wang resin (~0.96 mmol/g) from Bachem. Both resins are based on 1% cross-linked divinylbenzene styrene copolymer (100−200 mesh). PyBrOP was purchased from Nova Biochem and HOAt from PerSeptive Biosystems, Inc. All other commercially available chemicals were of *puris p.a.* quality and used without further purification. The oxazolidinones **1** and **3** were prepared according to ref 6a. RP-HPLC was performed using a Vydac RP-C18 column with a linear gradient of CH_3CN/0.1% TFA (30−100% over 30 min) in water/0.1% TFA at a flow rate of 0.8 mL/min and monitoring at 230 and 254 nm. ^1H and ^{13}C NMR were recorded at 300 and 75 MHz. Mass spectral data were obtained by electrospray mass spectroscopy. FT-IR spectra were collected on a BIO-RAD, FTS-40 spectrophotometer coupled with a UMA-300 IR microscope, using a SPC-3200 data station. The microscope was equipped with a 36X Cassegrain objective and liquid nitrogen cooled mercury−cadmium−telluride (MCT) detector.[9a] Flattened bead was used throughout the experiments.[9b] IR spectra were normalized by making the intensity of a polystyrene band at 1947 cm^{-1} equal. The areas under the typical band of the product at 1800 cm^{-1} were integrated. The values of integration were plotted against time. These data points were fitted to a rate equation for a pseudo-first-order reaction[9c] by using the nonlinear regression program SigmaPlot for Windows (Jandel Scientific, San Rafael, CA).

(*S*)-(Allyloxycarbonyl)-5-oxo-4-oxazolidineacetic Acid (2).[14] According to ref 6a, Alloc-Asp-OH (18.0 g, 82.9 mmol), paraformaldehyde (14.42 g, 165.8 mmol), and *p*-TsOH·H_2O (0.95 g, 5.0 mmol) in benzene (420 mL) were refluxed with H_2O removal (Dean−Stark apparatus) for 3 h. The resulting solution was diluted with AcOEt (50 mL), washed with 0.3 M K_2CO_3 (20 mL) and H_2O (3 × 25 mL), and concentrated *in vacuo* to give **2** (18.25 g, 92% yield) as a viscous oil: $[\alpha]^{rt} = +153.5$ ($c = 1.02$, $CHCl_3$); IR (KBr) 1810, 1722 cm^{-1}; ^1H NMR ($CDCl_3$) 3.09 (dd, 1H, $J = 3.1$, 18.2 Hz), 3.3 (s br., 1H), 4.36−4.39 (m, 1H), 4.60−4.72 (m, 2H), 5.27−5.36 (m, 3H), 5.52 (s br, 1H), 5.86−5.99 (m, 1H), 10.16 (s br, 1H); ^{13}C NMR ($CDCl_3$) 34.15, 51.47, 67.09, 78.49, 119.12, 131.46, 152.76, 171.70, 174.69; MS (MH^+, *m*/*z*) 330. Anal. Calcd for $C_9H_{11}NO_6$: C, 47.17; H, 4.84; N, 6.11. Found: C, 47.15; H, 4.58; N, 5.92.

Representative Procedure for Coupling to the Resin.[15] **Polymer-Bound Oxazolidinone 5.** Fmoc−Knorr resin (10.7 g, 8.35 mmol, 0.78 mmol/g) was first washed with CH_2Cl_2 and NMP and Fmoc-deprotected with 20% piperidine in NMP (75 mL) for 10 min, and the resin was then drained and treated with fresh 20% piperidine in NMP (75 mL) for 20 min. The resin was washed with NMP (5 × 75 mL) for 10 min. Separately, oxazolidinone **2** (2.85 g, 12.53 mmol) was dissolved in NMP (150 mL) and treated with PyBrOP (5.84 g, 12.53 mmol), HOAt (1.67 g, 12.53 mmol), and DIEA (6.55 mL, 37.56 mmol). The yellow solution was then added to the resin. The mixture was agitated by bubbling N_2 through the suspension. After 3 h, the Ninhydrin test[16] was negative, and so the resin was washed with NMP (3 × 100 mL, 10 min), NMP/CH_2Cl_2 1:1 (2 × 100 mL, 10 min), and CH_2Cl_2 (2 × 100 mL, 10 min) and dried under *vacuo* to give resin **5** (11.15 g). The loading was determined by microanalysis (N, 2.99%): 0.71 mmol/g.

Representative Procedure for Reaction with Amines. Preparation of Cbz Asn Amide 8. The resin **4** (300 mg, 0.227 mmol) was suspended in DMF (5 mL), and phenethylamine (270 μL, 2.13 mmol) was added. The suspension was mixed by shaking for 20 h. The resin was then washed with DMF, THF, and CH_2Cl_2 and dried *in vacuo* to give 311 mg of polymer-bound Asn amide. FT-IR on bead showed no oxazolidinone at 1800 cm^{-1}. Cleavage was performed by stirring the resin (310 mg) with 3 mL of TFA/H_2O 95:5 for 30 min. The resin was removed by filtration and washed with TFA/H_2O and CH_3CN, and the solvents were evaporated. The residue was treated with Et_2O, evaporated, and dried under vaccuo to give **8** (65 mg, 80% yield) as a white powder: RP-HPLC $t_R = 12.6$ min; IR (KBr) 1688, 1649 cm^{-1}; ^1H NMR (DMSO-d_6) 2.3−2.5 (m, 2H), 2.65−2.75 (m, 1H), 3.2−3.3 (m, 2H), 4.3−4.35 (m, 1H), 5.05 (s, 2H), 7.15−7.4 (m, 10 H); ^{13}C NMR (DMSO-d_6) 35.1, 37.4, 51.7, 65.5, 126.1, 127.7, 127.8, 128.3, 128.7, 137.0, 139.5, 155.7, 171.0, 171.3; MS (MH^+, *m*/*z*) 370.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds **8**−**19** and their corresponding HPLC profiles, single "flattened" bead FT-IR spectra of compounds **4**−**7** and their reaction products leading to compounds **8**−**19**, and the plotted data obtained on the FT-IR reaction monitoring (37 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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(14) We are unable to extract coupling constants for the allylic protons as they are overlapped with the proton of the oxazolidinone.

(15) Solid-phase-resin reactions were mixed by nitrogen sparge through sintered glass fritted reaction vessels.

(16) (a) Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595−599. (b) Sarin, V.; Kent, S.; Tam, J.; Merrifield, B. *Anal. Biochem.* **1981**, *117*, 147−157.