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Solid phase synthesis of 1-substituted pyroglutamates

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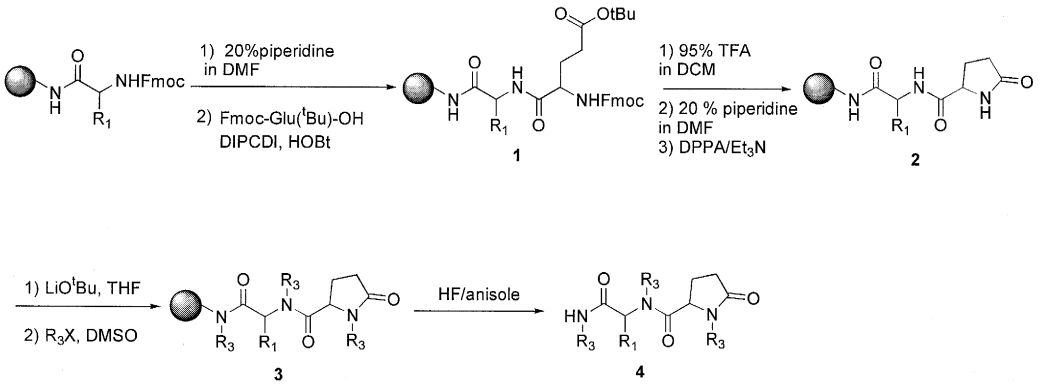
Abstract

Starting from a dipeptide containing the ^{t}Bu ester of glutamic acid, disubstituted 2-pyrrolidinones were prepared in good yield and high purity. Cyclization takes place using DPPA as activating reagent. Diversity was achieved through reductive alkylation of the starting dipeptide and *N*-alkylation following the cyclization step. This approach has been used for the synthesis of both individual compounds and mixture-based combinatorial libraries.

Substituted 2-pyrrolidinone derivatives are an important class of nitrogen-containing heterocycles.[1] They possess a variety of biological activities,[2] including the treatment of brain and cognitive problems,[3] anticolvulsant agents,[4] and also as inhibitors of HIV-1 replication.[5] In organic synthesis they have proven to be effective intermediates in the synthesis of alkaloids and γ-amino acids,[6] their corresponding pyrrolidines,[7] and as chiral auxiliaries in the synthesis of α-amino acids.[8]



Scheme 1. Solid phase synthesis of 1,5-disubstituted 2-pyrrolidinones

Although there are many reports describing the synthesis of pyrrolidinones in solution,[7] only one report describes the synthesis of this class of compound on the solid phase.[9] In our continuous efforts

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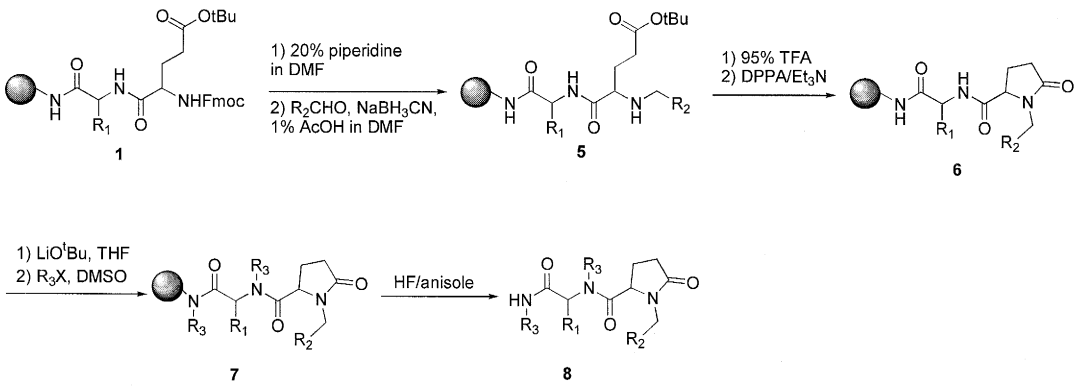
toward the development of new combinatorial libraries of small molecules and heterocycles starting from peptides,[10] we describe here the solid phase synthesis of 1,5-disubstituted 2-pyrrolidinones.



Scheme 2. Strategy for introducing one or more diversity positions in disubstituted pyrrolidinones

The strategy used is similar to that reported for the synthesis of 2,3-disubstituted succinimides.[11] Starting from *p*-methylbenzydrylamine (MBHA) resin-bound Fmoc-amino acid, the Fmoc group is cleaved with a solution of piperidine in DMF and the resultant free amine is coupled to Fmoc-glutamic acid-ɣ-^{t}Bu ester using standard SPPS. Following deprotection of the ^{t}Bu ester and the Fmoc protecting group, the resin-bound dipeptide was treated with diphenylphosphorylazide (DPPA), to yield the 5-substituted-2-pyrrolidinones **2** (Scheme 1). A similar product has been reported by Lazato et al. during the performance of the Curtius reaction of Boc-Glu-OMe with DPPA and triethylamine.[12] In the case described herein, no triethylamine was necessary for completion of the reaction. Treatment of the resin-bound **2** with an alkylating reagent in the presence of lithium *tert*-butoxide,[13] followed by HF cleavage, led to the 1,5-disubstituted-2-pyrrolidinones **4**, having two positions of diversity.

Table 1
Individual pyrrolidinones

Compound	R_1	R_2	R_3	Mass	Mass	Yield**
2a*	Bzl			275.30	276.0	80.7%
2b*	$CH_2CH(CH_3)_2$			241.29	242.0	88.7%
2c*	CH_3			199.21	200.0	96.4%
4a	Bzl		CH_3	317.38	318.1	100%
4b	$CH_2CH(CH_3)_2$		CH_3	283.37	284.1	100%
4c	CH_3		CH_3	241.29	242.0	77.1%
4d	Bzl		Allyl	395.49	396.3	79.2%
4e	$CH_2CH(CH_3)_2$		Allyl	361.48	362.3	75.5%
4f	CH_3		Allyl	319.40	320.1	93.3%
6a*	Bzl	Furyl		355.39	356.2	73.2%
6b*	$CH_2CH(CH_3)_2$	Bzl		331.41	332.2	86.9%
6c*	CH_3	Bzl		289.33	290.0	100%
8a	Bzl	Furyl	CH_3	383.44	384.1	79.3%
8b	$CH_2CH(CH_3)_2$	Bzl	CH_3	359.46	360.1	95.7%
8c	CH_3	Bzl	CH_3	317.38	317.9	83.8%

* After cleavage from the resin. ** Yields of the crude were determined according to the loading of the resin.

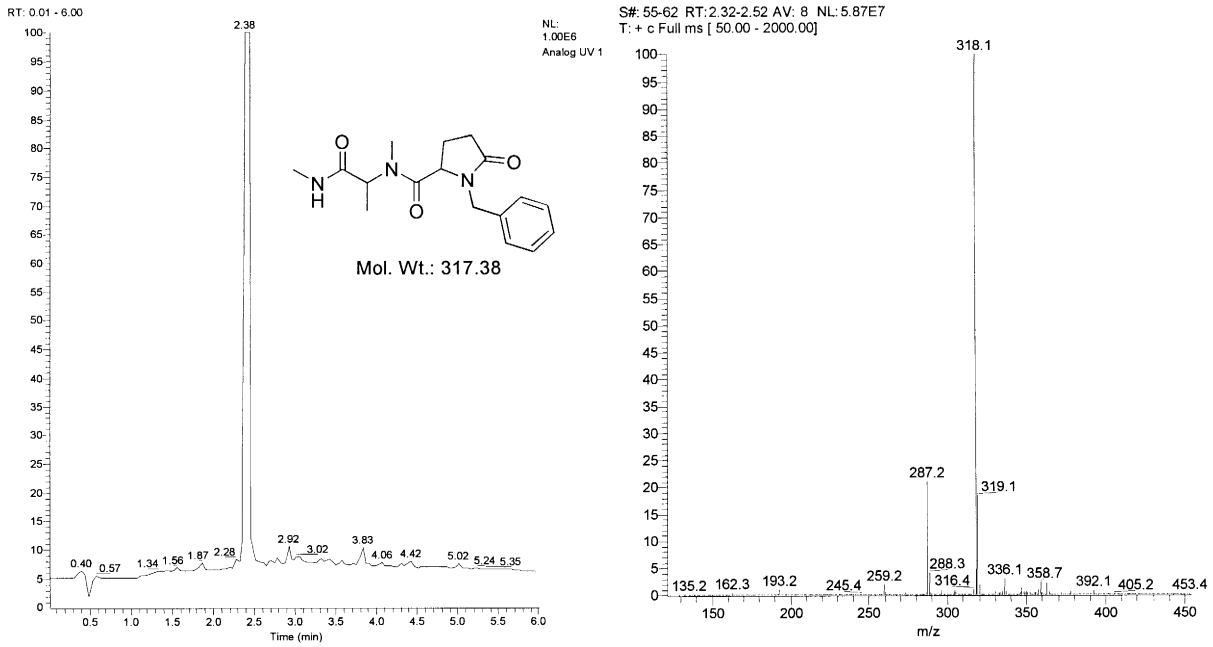


Fig. 1. Representative LC–MS for pyrrolidinone **8c**

In order to increase the diversity of the substitution pattern in this product, we explored a modification in the strategy (Scheme 2). Starting from **1**, and following Fmoc cleavage, the primary amine is reductively alkylated in the presence of aldehyde and sodium cyanoborohydride leading to **4**. Removal of the ^{t}Bu group and reaction with DPPA and triethylamine yielded the 1,5-disubstituted 2-pyrrolidinones **5**, which can be alkylated under the same conditions as described above to yield **6** having additional diversity.[14]

Using the parallel synthesis approach known as the 'tea bag' method,[15] 15 individual compounds were synthesized. All compounds were obtained with high purity and good yield (Table 1) and were characterized by LC–MS. Fig. 1 shows the LC–MS spectra of the compound **8c** derived from alanine, benzaldehyde and methyl iodide. The starting pyrrolidinone **2a** was also characterized by NMR spectroscopy (^{1}H and ^{13}C NMR).[16]

Acknowledgements

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14. Synthetic procedure: 50 mg of MBHA resin (1 meq/g, 100–200 mesh) was placed in a polypropylene mesh packet. After neutralization with 5% of DIEA in DCM, the first Fmoc amino acid (6 equiv.) was coupled in the presence of HOBT (6 equiv.) and DIPCDI (6 equiv.). After removal of the Fmoc protecting group with a solution of 20% piperidine in DMF (20 min.), the ^{t}Bu ester of Fmoc-Glutamic acid was coupled in the same conditions. Following Fmoc removal, the reductive alkylation was accomplished by addition of the aldehyde (5 equiv., 0.1 M) in 1% AcOH in DMF, followed by addition of $NaBH_3CN$ (5 equiv.). The ^{t}Bu ester was deprotected with 95% TFA in DCM for 30 min. After neutralization, the cyclization takes places by adding DPPA (6 equiv.) and NEt_3 (6 equiv.) in THF, and heating at 70°C overnight (for compounds **2** and **3**, Et_3 wasn't necessary). The alkylation was achieved using the protocol previously described.[13] Cleavage from the resin with HF:anisole (95:5), and extraction with acetic acid (95%), followed by lyophilization, yielded the desired products.
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16. ^{1}H NMR (500 MHz, DMSO-d_6): 1.42 (m, 1H), 1.96 (m, 1H), 2.05 (m, 1H), 2.74 (dd, J_{HH}=10.1 Hz, J=3.5 Hz, 1H), 3.04 (dd, J_{HH}=13.7 Hz, J_{HH}=4.5 Hz, 1H), 3.98 (dd, J_{HH}=8.4 Hz, J_{HH}=4.1 Hz, 1H), 4.50 (m, 1H), 7.17 (s, 1H), 7.19 (m, 5H), 7.49 (s, 1H), 7.69 (s, 1H), 8.13 (d, J_{HH}=8.8 Hz, 1H). ^{13}C NMR (500 MHz, DMSO-d_6): 25.27 (CH_2), 29.12 (CH_2), 37.87 (CH_2), 53.33 (CH), 55.39 (CH), 126.23 (CH), 127.97 (CH), 129.28 (CH), 137.88 (C), 171.98 (C=O), 172.90 (C=O), 177.35 (C=O).