Pergamon

Tetrahedron Letters, Vol. 38, No. 28, pp. 4943-4946, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01086-1

SOLID PHASE SYNTHESIS OF 1,3,4,7-TETRASUBSTITUTED PERHYDRO-1,4-DIAZEPINE-2,5-DIONES

Adel Nefzi, John M. Ostresh and Richard A. Houghten*

Torrey Pines Institute for Molecular Studies, 3550 General Atomics Ct., San Diego, CA 92121 USA

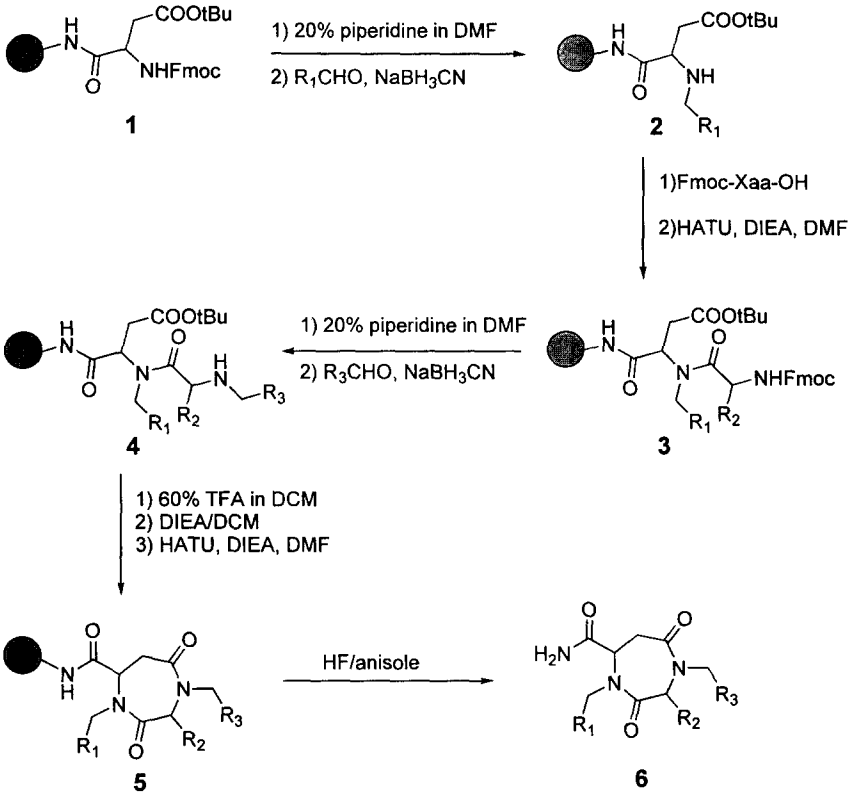
Abstract: The solid phase synthesis of 1,3,4,7-Tetrasubstituted Perhydro-1,4-diazepine-2,5-diones is described. Starting from the resin-bound tBu ester of aspartic acid and employing reductive alkylation and amide formation, 40 diazepines have been synthesized in good yield and high purity. The general nature of this approach permits not only large numbers of individual diazepines to be prepared, but also combinatorial libraries. © 1997 Elsevier Science Ltd.

Due to their versatility, amino acids have been used extensively for the synthesis of heterocyclic compounds.[1] Furthermore, their activation, protection and deprotection are well documented.[2]

In our ongoing efforts directed toward the solid phase synthesis of small molecule and heterocyclic compounds and the generation of combinatorial libraries of organic compounds using amino acids and peptides as starting materials,[3] we report here the design and solid phase synthesis of diazepines derived from resin-bound aspartic acid. We believe that this family of derivatives offers a uniquely useful structure for the discovery of new, biologically active compounds.

Our synthetic approach is illustrated in Scheme 1. The solid phase synthesis of diazepine derivatives is initiated by reduction with $NaBH_3CN$ in 1% AcOH in DMF of the enamine formed by the reaction product between an aldehyde and the α-amino group of the p-methylbenzhydrylamine resin-bound aspartic acid. No racemization has been observed when the resulting imine is reduced immediately upon formation.[4] The coupling of an Fmoc amino acid to the resulting secondary amine does not readily go to completion. This same difficulty was previously described by Krchňák and co-workers for the solid phase synthesis of 2,5-disubstituted dioxopiperazines.[5] Satisfactory results were obtained using double coupling with HATU.[6] This coupling step depends strongly on the incoming amino acid.[7] Good yields were obtained with Phe and Met(O), whereas low yields were obtained with hindered amino acids such as Val.

Once the dipeptide has been formed, the Fmoc protecting group is removed and a second reductive alkylation is carried out using the same conditions. Following tBu cleavage, the thermodynamically favorable coupling of the resulting secondary amine to the side chain of aspartic acid was readily accomplished in the presence of HATU.

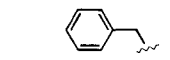
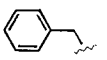
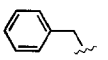
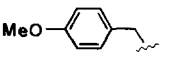
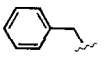
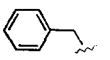
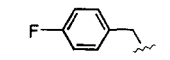
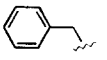
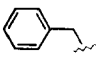
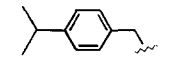
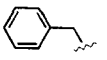
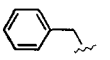
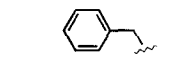
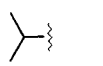
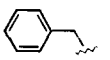
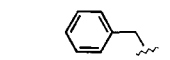
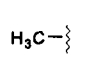
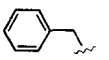
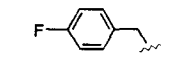
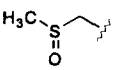
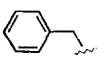
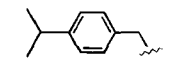
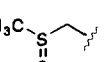
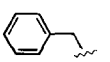


Scheme 1. Solid phase synthesis of 1,3,4,7-Tetrasubstituted Perhydro-1,4-diazepine-2,5-diones using aspartic acid as starting material.

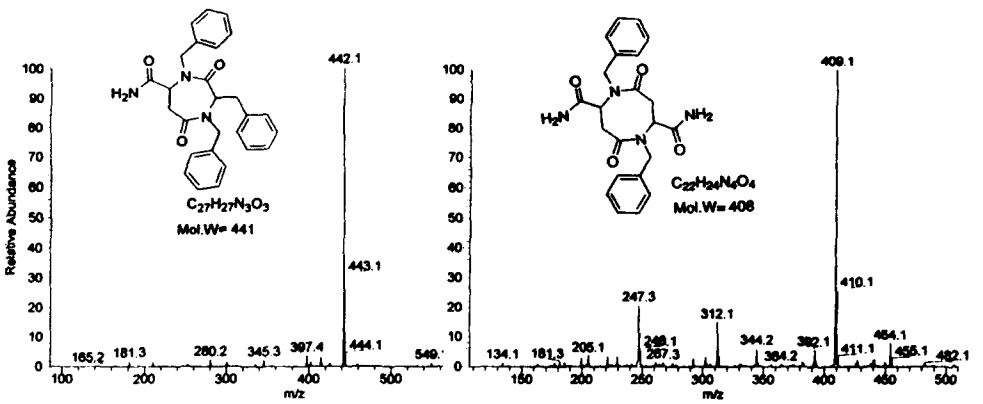
Dimerization of the unreacted N-substituted aspartic acid (i.e., compound **2** minus the tBu) was obtained as a byproduct (5-15%). This yielded the eight-membered cyclic dipeptidomimetic. Employing the above strategy and using the simultaneous parallel synthesis approach (T-bag technology),[8,9] we synthesized 40 different diazepines with HPLC purities ranging from 15 to 87%. Examples are shown in Table 1. All of the compounds prepared were characterized by RP-HPLC, LCQ-Mass spectra and ^{1}H-NMR. In those cases in which low yields were obtained, the major product found was the dialkylated amine resulting from a second reduction with R_3CHO and $NaBH_3CN$ alkylation of any remaining secondary amine from unreacted **2**.

In Scheme 2, we show the LCQ-MS spectra of the major peak corresponding to the desired product: the diazepine **6a** derived from (R1= R2 = R3= benzyl), with the expected mass (MH^+= 442); and the MS spectra of the minor peak corresponding to the cyclic dipeptidomimetic **7a** resulting from the dimerization of the N-benzylated aspartic acid (MH^+= 409).[10]

Table 1.

Compound #	R_1	R_2	R_3	HPLC purity, %
6a				72
6b				85
6c				87
6d				80
6e				15
6f				52
6g				62
6h				56

The products were run on a Vydac column, gradient 5 to 95% of 0.05% TFA in ACN in 7 min. The purity was estimated on analytical traces at 214 nm.



Scheme 2: LCQ-Mass spectra of **6a** and **7a**.

Acknowledgments

We thank Jutta Eichler for helpful discussion, Edward Brehm for analytical support and Eileen Weiler for editorial assistance. This work was funded by National Science Foundation Grant No. CHE-9520142 and by Houghten Pharmaceuticals, Inc., San Diego, Calif.

References and Notes

1. For a review, see a) Sardina, F. M.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825. b) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449.
2. Barany, G.; Merrifield, R.B. In *The Peptides: Analysis, Synthesis, Biology, Vol. 2*, Gross, E.; Meienhofer, J. Eds.; Academic Press, New York, **1979**, pp. 1-284.
3. Nefzi, A.; Ostresh, J. M.; Meyer, J-P.; Houghten, R. A. *Tetrahedron Lett.* **1996**, *38*, 931.
4. Ho, P. T.; Ngu k.-Y. J. Org. Chem. **1993**, *58*, 2313.
5. Krchňák, V.; Weichsel, A. S.; Cabel, D.; Lebl, M. In *Molecular Diversity and Combinatorial Chemistry: Libraries and Drug Discovery*, Chaiken, I. M.; Janda, K. D. Eds.; American Chemical Society, Washington, DC, **1996**; pp. 99-117.
6. Carpino, L. A.; El-Faham, A.; Minor, C. A.; Albericio, F. *J. Chem. Soc., Chem. Commun.* **1994**, 201.
7. Ostresh, J. M.; Winkle, J. H.; Hamashin, V. T.; Houghten, R. A. *Biopolymers.* **1994**, *34*, 1681.
8. Houghten, R. A. *Proc Nat Acad Sci.* USA. **1985**, *82*, 5131.
9. Houghten, R. A.; Bray, M. K.; DeGraw, S. T.; Kirby, C. J. *Int. J. Pep. Prot. Res.* **1986**, *27*, 673.
10. *Typical procedure for the synthesis of individual diazepine* **6a**: 100 mg of MBHA resin was contained in a polypropylene mesh packet (T-bag).[7] The resin was neutralized with 5% DIEA in DCM. Aspartic acid was coupled in the presence of DICI/HOBt. Following the removal of Fmoc with 20% piperidine in DMF, benzaldehyde (5 eq, 0.07M) was added in 1% AcOH in DMF, followed immediately by the addition of $NaBH_3CN$ (5 eq). During the reductive alkylation, a small amount (5 to 8%) of dialkylation is always observed. The desired secondary amine was coupled twice (4 hours and overnight) with phenylalanine (5 eq), HATU (5eq) and DIEA (5eq) in DMF. Following Fmoc removal, a second reductive alkylation was performed as described above. The tBu group was cleaved with a solution of TFA in DCM, and the generated secondary amine was coupled to the side chain of aspartic acid in the presnce of HATU (3 eq) and DIEA (3 eq) in DMF. Following cleavage of the resin with HF/anisole (95/5), the desired product was extracted with acetonitrile/water (50/50), and lyophilized to afford a white powder. The product was characterized by ^{1}H-NMR and LCQ-MS.

(*Received in USA* 22 *April* 1997; *accepted* 9 *May* 1997)