Pergamon

Tetrahedron Letters, Vol. 37, No. 7, pp. 937-940, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02395-X

Solid Phase Synthesis of Hydantoins Using a Carbamate Linker and a Novel Cyclization / Cleavage Step

Bruce A. Dressman*, Larry A. Spangle, and Stephen W. Kaldor

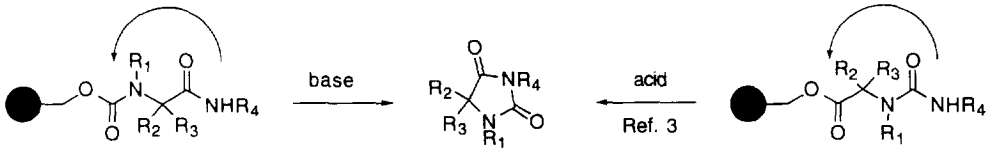
Lilly Research Laboratories
Lilly Corporate Center
Indianapolis, IN 46285

Key Words: solid phase synthesis, combinatorial chemistry, hydantoin, cyclization, carbamate

Abstract: An 800 compound hydantoin library has been constructed using a diverse set of 20 amino acids and over 80 primary amines. Amino acids were attached via their N-termini to hydroxymethyl polystyrene using a carbamate linker. Bound amino acids were converted to their corresponding amides and then cyclized under basic conditions to give hydantoins in high purities.

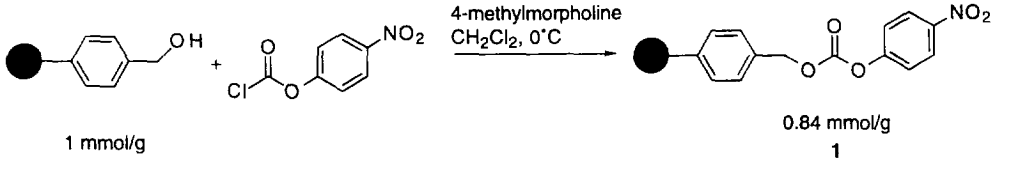
Recently, a considerable amount of attention has been focused on the use of solid phase synthesis (SPS) for the generation of combinatorial libraries of non-oligomeric, small organic compounds for biological screening.[1] To date, syntheses of a variety of classes of heterocycles have been reported using SPS methodology.[2] A method for the SPS of hydantoins has been described by Hobbs DeWitt in which amino acid intermediates are attached to a solid support through a C-terminal ester linkage.[3] We wish to describe here a novel method for the SPS of hydantoins which employs N-terminal amino acid attachment and a base-catalyzed cyclization / cleavage strategy (Scheme 1).

Scheme 1



Use of a carbamate linker to attach amino acids via their N-terminus to polystyrene was first reported by Letsinger for the synthesis of dipeptides.[4] Letsinger's original method for attachment of amino acids involved the use of a resin bound chloroformate which was generated from phosgene and hydroxymethyl polystyrene. Attempts to use this linking agent in our laboratory proved unsatisfactory for library synthesis due to its water and air sensitive nature. This led to the use of activated carbonate **1** which had been previously reported by Leznoff for the synthesis of unsymmetrical diamines (Scheme 2).[5] It was found that hydroxymethyl polystyrene[6] (1

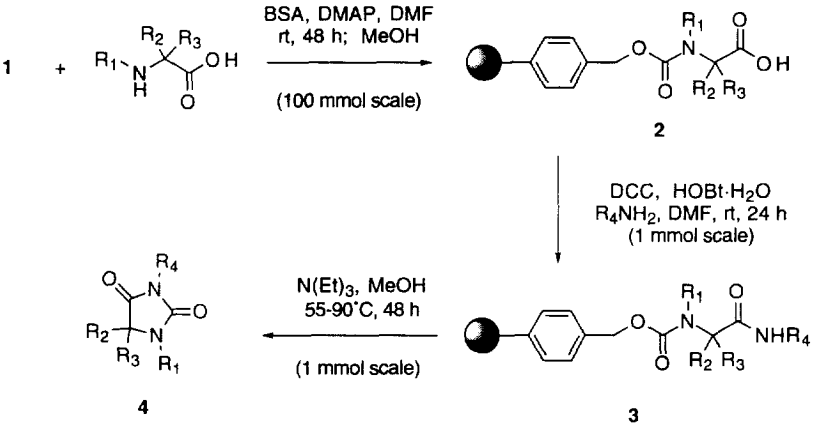
Scheme 2



mmol/g) could be readily converted to **1** using N-methyl morpholine (2.0 eq) and *p*-nitrophenyl chloroformate (2.0 eq) in nearly quantitative yield (>95%) as analyzed by gel phase ^{13}C NMR (elemental analysis for nitrogen gave a loading capacity of 0.84 mmol/g).[7] Activated carbonate **1** is a robust polymer-bound reagent well-suited for combinatorial library production: it can be produced on large scale (>100 g) and stored for at least 6 months without loss of activity.

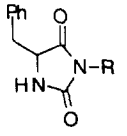
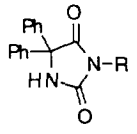
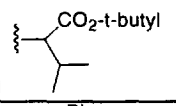
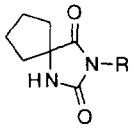
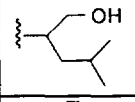
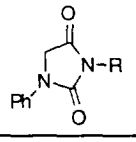
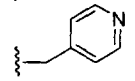
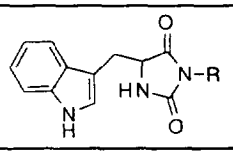
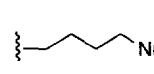
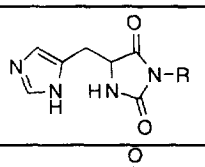
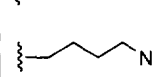
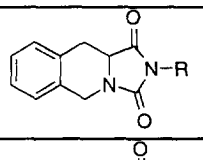
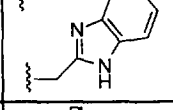
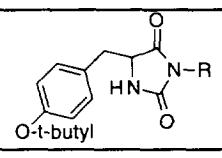
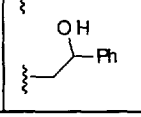
The general method for the synthesis of hydantoins is shown in Scheme 3. Selected amino acids (4 eq) were dissolved with light heating in DMF using N,O-bis(trimethylsilyl)acetamide (BSA; 10 eq) and then coupled with activated carbonate **1** in the presence of DMAP (2 eq) to obtain the free acid resin-bound intermediate **2**. For a given amino acid, intermediate **2** was typically constructed on 100 mmol scale in batch mode to provide a large feedstock for library construction. Amide formation was then carried out overnight on a 1 mmol scale using standard carbodiimide coupling conditions with an excess of primary amine (4 eq), HOBt•H_2O (4 eq) and DCC (4 eq). Treatment of resin intermediate **3** with excess triethylamine (14 eq) in methanol for 48 h at temperatures between 55-90°C afforded hydantoins (**4**). Acetonitrile can also be used as a substitute for methanol but lower yields and product purities are generally observed. Attempts to use other protic solvents such as isopropyl and ethyl alcohol were surprisingly unsuccessful. Gel phase ^{13}C NMR spectrometry proved a valuable tool for both pilot experiments and quality control in library production mode.

Scheme 3



Using this methodology, a library of 800 individual hydantoins was synthesized using 20 amino acids and over 80 primary amine building blocks. A notable feature of this chemistry is the relatively diverse set of amino acid building blocks that are tolerated: polar, non-polar, acyclic, cyclic, geminally disubstituted, N-alkyl, and N-aryl amino acids are all successfully employed. Furthermore, in contrast to the previously reported SPS of hydantoins, which relies on isocyanates for diversity at R_4 (<300 commercially available, majority aromatic or aliphatic), the route outlined in this Letter utilizes primary amines and anilines (>3000 commercially available). A random analytic sampling of 15% of the library using FD MS showed that in 90% of the cases desired product was obtained. A few representative structures of hydantoins contained in the library that have been characterized by FD MS, HPLC and / or ^1H NMR are shown in Table 1.

Table 1. Representative Structures, Cyclization Temperatures, Mass Recoveries, HPLC Purities and Retention times for the Hydantoin Library

Hydantoin Scaffold	R	Cyclization Temp.(°C)	% Mass Recovery[a]	HPLC Purity[8]	Retention Time(min)
		90	57%[9]	99%	20.2
		90	64%	97%	23.8
		90	40%	99%	23.1
		90	24%	99%[b]	25.4
		90	70%	65%	19.0
		90	76%	74%	17.9
		90	12%	90%	22.0
		90	15%	95%	15.5
		90	73%	NA	NA
		90	42%	67%	17.7
		90	74%	71%	13.7
		90	34%	74%	15.4
		60[10]	38%	91%	22.1
		60	34%	76%	17.4
		90	57%	99%	22.6
		90	59%	99%	21.2

a) Mass recoveries are based on the theoretical recovery of product starting from 1 mmol/g hydroxymethyl polystyrene over 4 steps. b) No transesterification was detected by ^{1}H NMR or FD MS.

In conclusion, an efficient process for the SPS of hydantoins has been developed which uses a novel cyclization /cleavage strategy. A sizable library of hydantoins has been constructed and is currently being screened for biological activity. Syntheses of additional classes of heterocycles using a similar cyclization / cleavage strategy are currently under investigation and will be reported separately.

Acknowledgements. We thank Kevin McLeaster and Ken Tranbarger for their help in equipment design and construction.

References and Notes

1. (a) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385-1401. (b) Baum, R. M. *Chem. Eng. News* **1994**, *72* (6), 20-26. (c) Amato, I. *Science* **1992**, *257*, 330-331.

2. (a) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *30*, 8135-8173. (b) Gordon, D. W.; Steele, J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 47-50. (c) Bunin, B. A.; Plunkett, M. J.; Ellman, J. A. *Proc. Natl. Acad. Sci* **1994**, *91*, 4708-4712. (d) Pei, Y.; Moos, W. H. *Tetrahedron Lett.* **1994**, *35*, 5825-5828. (e) Beebe, X.; Schore, N. E.; Kurth, M.J. *J. Org. Chem.* **1995**, *60*, 4196-4203. (f) Beebe, X.; Chiappari, C. L.; Olmstead, M. M.; Kurth, M. J.; Schore, N. E. *J. Org. Chem.* **1995**, *60*, 4204-4212. (g) Murphy, M. M.; Schullek, J. R.; Gordon, E. M.; Gallop M. A. *J. Am. Chem. Soc.* **1995**, *117*, 7029-7030. (h) Pátek, M.; Drake, B.; Lebl, M. *Tetrahedron Lett.* **1995**, *36*, 2227-2230. (i) Wipf, P.; Cunningham, A. *Tetrahedron Lett.* in press.

3. Hobbs DeWitt, S. W.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Reynolds Cody, D. M.; Pavia, M. R. *Proc. Natl. Acad. Sci.* **1993**, *90*, 6909-6913.

4. (a) Letsinger, R. L.; Kornet, M. J.; Mahadevan, V.; Jerina, D. M. *J. Am. Chem. Soc.* **1964**, *86*, 5163-5165. (b) Letsinger, R. L.; Kornet, M. J. *J. Am. Chem. Soc.* **1963**, *85*, 3045-3046. (c) Felix, A. M.; Merrifield, R. B. *J. Am. Chem. Soc.* **1969**, *92*, 1385-1391.

5. (a) Dixit, D. M.; Leznoff, C. C. *Isr. J. Chem.* **1978**, *17*, 248-252. (b) Dixit, D. M.; Leznoff, C. C. *J. Chem. Soc. Chem.Commun.* **1977**, 798-799. (c) More recently a method for the synthesis of tripeptides has been reported which uses a polymer bound acyl imidazole as a way of forming carbamate linkers: Hauske, J. R.; Dorff, P. *Tetrahedron Lett.* **1995**, *36*, 1589-1592.

6. 1% cross linked hydroxymethyl polystyrene (1 mmol/g) was purchased from Bachem California.

7. Preparation of activated carbonate **1**: *p*-Nitrophenyl chloroformate (1.31 g, 6.5 mmol) was added in one portion to a stirring solution of hydroxymethyl polystyrene (3.26 g) and N-methyl morpholine (659 mg, 6.5 mmol) in methylene chloride at 0°C. The reaction mixture was warmed to room temperature, stirred overnight, filtered and washed with methylene chloride. Drying overnight in a vacuum oven gave 3.28 g of a light pink resin. ^{13}C NMR ($CDCl_3$) δ 70.96 (broad s, P-CH_2O-). IR (KBr) 1761 cm^{-1}. Gel Phase ^{13}C were obtained using the procedure of Giralt (Giralt, E.; Rizo, J.; Pedroso, E. *Tetrahedron* **1984**, *40*, 4141-4152).

8. Analysis by HPLC (8X10 cm Waters Nova-Pak C18 column with a 4 μm particle size, gradient elution 0-100% acetonitrile / water containing 0.1% TFA, 1 mL/ min for 30 min then 100% acetonitrile containing 0.1% TFA , 1 mL/ min for 10 min) by area integration at 220 nm.

9. An analytical sample was purified by radial chromatography (25-50% ethyl acetate/ hexane). ^1H NMR (300 MHz, $CDCl_3$) δ 2.88 (dd, J = 14.0, 8.4 Hz, 1H), 3.26 (dd, J = 17.9, 3.9 Hz, 1H), 4.22-4.32 (m, 1H), 4.55-4.70 (m, 2H), 5.75 (br s, 1H), 7.10-7.30 (m, 10H). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.54; H, 5.68; N, 9.90. Ionspray MS (M+1, 100) 281.1.

10. Cyclic amino acid scaffolds were generally removed from the resin at lower temperature in order to reduce the amount of a methanol ring opened by-product.

(*Received in USA* 15 *October* 1995; *accepted* 1 *December* 1995)