Pergamon

Tetrahedron Letters 39 (1998) 8199–8202

TETRAHEDRON LETTERS

EFFICIENT SOLID PHASE SYNTHESIS OF 3,5-DISUBSTITUTED HYDANTOINS

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Received 24 July 1998; revised 24 August 1998; accepted 27 August 1998

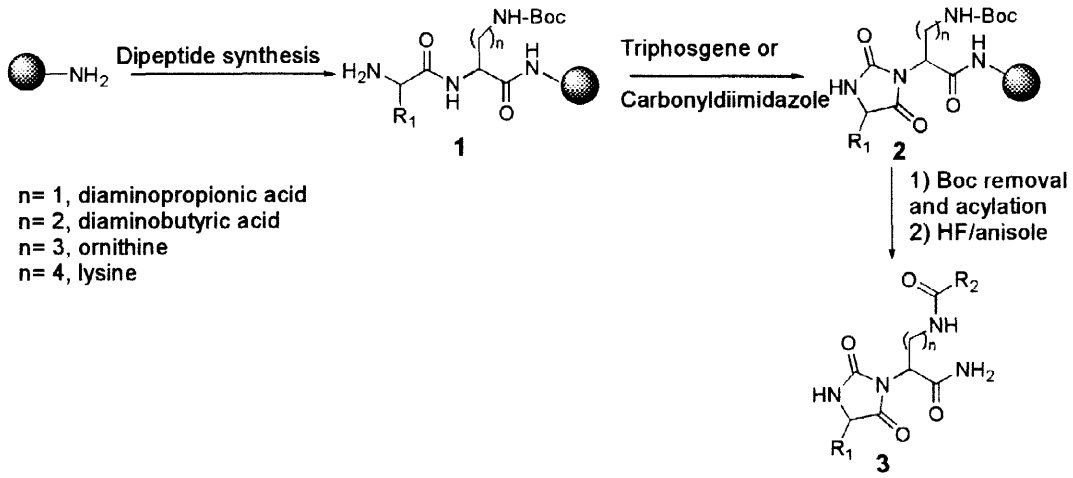
Abstract: An efficient solid phase synthesis of 3,5-disubstituted hydantoins is described. The treatment of a resin-bound diamino acid containing dipeptide with carbonyldiimidazole or triphosgene afforded the five member ring hydantoins. A second site of diversity is included following N-acylation of the free amine side chain with a wide range of commercially available carboxylic acids.

The development of new strategies for the generation of heterocyclic and small molecule organic compounds is of great value for the discovery of new, biologically active compounds.[1] A wide range of therapeutic properties have been reported for hydantoins and thiohydantoins, including antiviral, antibacterial, antifungal, herbicidal, anticonvulsant, antidiabetic, anti-inflammatory, antiulcer and antiarrhythmic activities.[2] New strategies for the synthesis of hydantoins and thiohydantoins continue to attract the interest of chemists and medicinal chemists.[3-5] We previously reported an efficient approach for the solid phase synthesis of individual and combinatorial libraries of hydantoins and thiohydantoins using resin-bound dipeptides as starting materials. Following the screening of these earlier libraries in a sigma competition assay using [^{3}H] pentazocine, individual hydantoins with high affinity binding were identified.[6] In order to increase the diversity of this class of compounds, we report here the solid phase synthesis of 3,5-disubstituted hydantoins.

The parallel synthesis of 3,5-disubstituted hydantoins was carried out on the solid phase using the "tea-bag" method.[7] The reaction scheme is illustrated in Scheme 1. Starting from a p-methylbenzhydrylamine resin-bound, orthogonally protected diamino acid (including diaminopropionic acid, diaminobutyric acid, ornithine or lysine), and following deprotection of the α-amino group and coupling of a second amino acid, the resin was treated with carbonyldiimidazole or triphosgene to afford a highly active intermediate isocyanate, which undergoes an intramolecular cyclization leading to the hydantoin. The diamino acid side chain is then deprotected and the free amine goup is N-acylated with a range of carboxylic acids to yield the desired hydantoins following cleavage of the resin with hydrogen fluoride.[8]

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01874-7

We initially tested this approach using ornithine as the diamino acid, along with five different L-amino acids (Phe, Thr, Ala, Leu, Ser) and three different carboxylic acids (phenylacetic acid, cyclohexanecarboxylic acid, isovaleric acid). We successfully synthesized 15 individual compounds in good yield and high purity (Table 1). All compounds prepared were characterized by LC-MS and ^{1}H-NMR.



Scheme 1. Solid phase synthesis of branched hydantoins.

Figure 1 illustrates a typical LC-MS spectra of the hydantoin **3n** obtained from serine, ornithine and cyclohexanecarboxylic acid. The use of this approach for the identification of highly active hydantoins will be reported elsewhere. This is a further example of our ongoing efforts toward the solid phase synthesis of heterocyclic compounds using resin-bound peptides as starting materials.[9-11]

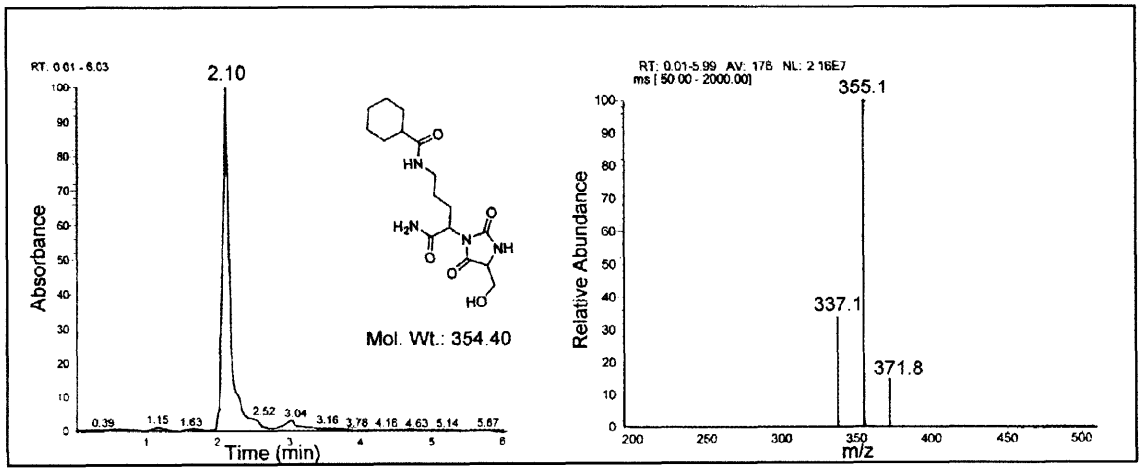
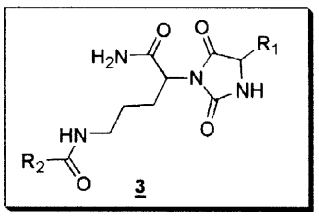


Figure 1. LC-MS of hydantoin **3n**.

Table 1. Individual hydantoins



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Entry	R_1	R_2	Purity	MW (calculated)	MW (found)
3a	$-CH_2$-Ph	$-CH_2$-Ph	90 %	422.5	423.1
3b	$-CH_2$-Ph	$-(C_6H_{11})$	92 %	414.5	415.2
3c	$-CH_2$-Ph	$-CH_2$-$CH(CH_3)_2$	91 %	388.5	389.1
3d	$-CH(CH_3)$-OH	$-CH_2$-Ph	93 %	376.4	377.1
3e	$-CH(CH_3)$-OH	$-(C_6H_{11})$	91 %	368.4	369.1
3f	$-CH(CH_3)$-OH	$-CH_2$-$CH(CH_3)_2$	89 %	342.4	343.1
3g	$-CH_3$	$-CH_2$-Ph	93 %	346.4	347.1
3h	$-CH_3$	$-(C_6H_{11})$	92 %	338.4	339.1
3i	$-CH_3$	$-CH_2$-$CH(CH_3)_2$	92 %	312.4	313.1
3j	$-CH_2$-$CH(CH_3)_2$	$-CH_2$-Ph	93 %	388.5	389.1
3k	$-CH_2$-$CH(CH_3)_2$	$-(C_6H_{11})$	87 %	380.5	381.2
3l	$-CH_2$-$CH(CH_3)_2$	$-CH_2$-$CH(CH_3)_2$	86 %	354.4	355.1
3m	$-CH_2$-OH	$-CH_2$-Ph	94 %	362.4	363.1
3n	$-CH_2$-OH	$-(C_6H_{11})$	92 %	354.4	355.1
3o	$-CH_2$-OH	$-CH_2$-$CH(CH_3)_2$	91 %	328.4	329.1

The products were run on a Keystone 053-715 column, 5 to 95%B (A: 0.05% TFA in H_20; B: 0.05% TFA in ACN) in 7 min. The purity was estimated on analytical traces at λ= 214 nm.

ACKNOWLEDGMENTS

We thank Eileen Weiler for editorial assistance. This work was funded by Trega Biosciences, Inc. and National Science Foundation Grant No. CHE-9520142 (Houghten).

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8) Typical procedure for the solid phase synthesis of individual hydantoins: 100 mg p-methylbenzydrylamine (MBHA) resin (1meq/g, 100-200 mesh) was contained within a sealed polypropylene mesh packet.[7] Reactions were carried out in a 10 ml polyethylene bottle. Following neutralization with 5% diisopropylethylamine (DIEA) in dichloromethane (DCM), the resin was washed with DCM. Fmoc-Orn(Boc)-OH was coupled using the conventional reagents hydroxybenzotriazole (HOBt) and diisopropylcarbodiimide (DICI). Following removal of the Fmoc group with 25% piperidine in DMF, a second Fmoc-amino acid was coupled under the same conditions. The Fmoc group was cleaved and the resin-bound dipeptide was treated with a 5-fold excess of triphosgene in the presence of DIEA (15-fold excess) in DCM anhydous or carbonyldiimidazole (15-fold excess). Following removal of the Boc group and neutralization of the free amino group with a solution of 5% DIEA in DCM, the amine was acylated with different carboxylic acids (10-fold excess) in the presence of 15 eq of DICI in DMF anhydrous overnight. Complete acylation was monitored by the Kaiser ninhydrin test.[12] The resin was then cleaved with anhydrous HF in the presence of anisole at 0 °C, and the desired product was extracted with a solution of acetonitrile/water (50:50) to afford the desired hydantoin following lyophilization.

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