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COMBINATORIAL CHEMISTRY OF HYDANTOINS

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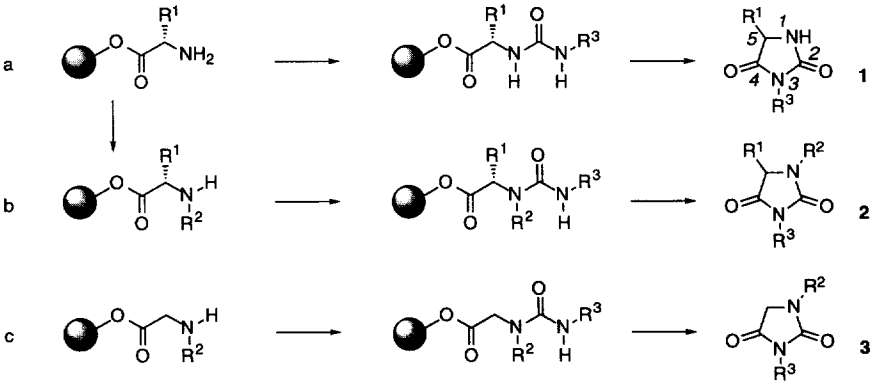
Abstract: Access to combinatorial chemistry of hydantoins is provided by convenient and versatile methods for the solid phase synthesis of libraries of 3,5-, 1,3- and 1,3,5-substituted hydantoins. The preparation of trisubstituted hydantoins features a Mitsunobu reaction for introduction of the substituent on N-1.

One of the many challenges in medicinal chemistry is to increase the affinity of a particular ligand for its receptor by reducing its degrees of freedom. This can be achieved for example by cyclization of a linear molecule. Another approach is to attach pharmacophoric groups to a relatively rigid scaffold molecule. With respect to this, especially interesting are scaffold molecules onto which functional groups can be introduced in combinatorial approaches. Examples of these scaffolds include diketopiperazines and the hydantoins. Therefore, it is not surprising that considerable attention has been directed to substituted diketopiperazines[1] and increasing attention is focused on hydantoins.[2] In view of this, we feel urged to publish our own results on the combinatorial chemistry of substituted hydantoins. While this work was in progress, reports appeared in which a substituent on hydantoin-N-1 was introduced by reductive amination.[2c–e] In this communication we describe the introduction of this substituent by starting from either a peptoid monomer, that is a N-substituted glycine derivative (route c, Scheme 1)[3] or by an alkylation procedure featuring a Mitsunobu reaction as was recently described by us (route b).[4] In addition, we found from the preparation of disubstituted hydantoins (route a and b) that cyclization/cleavage can be carried out under considerably milder conditions than thus far reported.[5]



Scheme 1. Combinatorial synthesis of hydantoins

The routes depicted in Scheme 1 allow for the introduction of substituents at **all** available ring positions viz. C-5, N-1, and N-3, in a variety of combinations. This enables the particularly interesting application of the rigid hydantoin ring as a scaffold for attachment of pharmacophoric groups.

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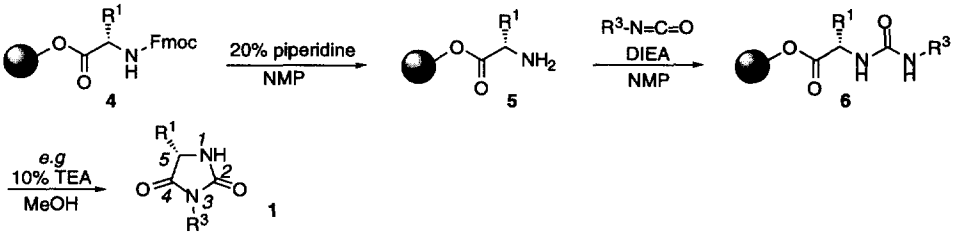
During our work on the solid-phase synthesis of urea peptides,[6] we discovered that cleavage of immobilized urea compounds from Tentagel®S-OH using mildly basic conditions resulted in the formation of cyclic hydantoins instead of the expected linear urea compounds. We took advantage of this not sought reaction, by developing it into a solid-phase synthesis method of hydantoins. According to the principle outlined in route a in Scheme 1, deprotection of the resin-attached amino acid[7] was followed by treatment with an isocyanate to give urea derivative **6**. Base-catalyzed cyclization/cleavage then gave 3,5-disubstituted hydantoins **1** (Scheme 2).

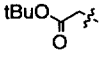
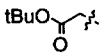
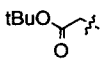
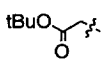
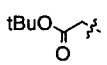
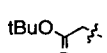
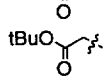
According to the literature,[2] strongly basic (or acidic) conditions, extended reaction times or elevated temperatures were required for formation of the hydantoin. However, we were able to accomplish the ring formation by a relatively short treatment (2–3 h) with mild base at room temperature. Several cleavage mixtures viz. 10% TEA/MeOH, a catalytic amount of KCN in MeOH, and $MeNH_2$ in THF proved to be effective for formation of the hydantoin. Surprisingly, treatment with 10% TEA/EtOH did not result in cyclization/cleavage. In this case, addition of a catalytic amount of KCN was essential. Fortunately, under the basic coupling conditions (DIEA/DCM) cyclization/cleavage did not take place at all.

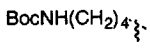
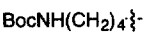
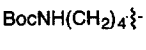
As a pilot experiment to investigate the applicability of the described procedure for combinatorial chemistry purposes, a six-member hydantoin library was constructed by parallel solid-phase organic synthesis, starting from two amino acids (Leu and Phe) and three isocyanates (isopropyl isocyanate, phenyl isocyanate and ethyl isocyanatoacetate). The hydantoins **1** were obtained in excellent yields (90–100%)[8,9] after column chromatography.

The size of this library could be readily expanded to a forty-two member hydantoin library, consisting of all possible combinations of six amino acids (i.e., Fmoc-Gly-OH, Fmoc-Phe-OH, Fmoc-Lys(Boc)-OH, Fmoc-Ser(OtBu)-OH, Fmoc-Asp(tBu)-OH, and Fmoc-Trp(Boc)-OH) and seven isocyanates (isopropyl, phenyl, benzyl, adamantyl, naphtyl, allyl isocyanate, and ethyl isocyanatoacetate) (Scheme 2, continued). In order to explore the scope and limitations of the procedure, we now included some isocyanates with bulkier side-chains (e.g., adamantyl and naphtyl isocyanate) which could be expected to give ring closure in a less straightforward manner. We also used amino acids with side-chains with functional groups. As references and to evaluate the reproducibility of the method, the hydantoins derived from phenylalanine, which were prepared in the first experiment, were also included in the library. The library was prepared in a MULTIBLOCK,[10] a device containing a 6 × 7 matrix of 42 fritted syringes, which are used as reaction vessels according to the procedure described above. Purification of the products was not necessary since the purity of the crude hydantoins, as assessed by TLC analysis, was generally very good.



Scheme 2. Solid-phase synthesis of 3,5-disubstituted hydantoins starting from amino acids

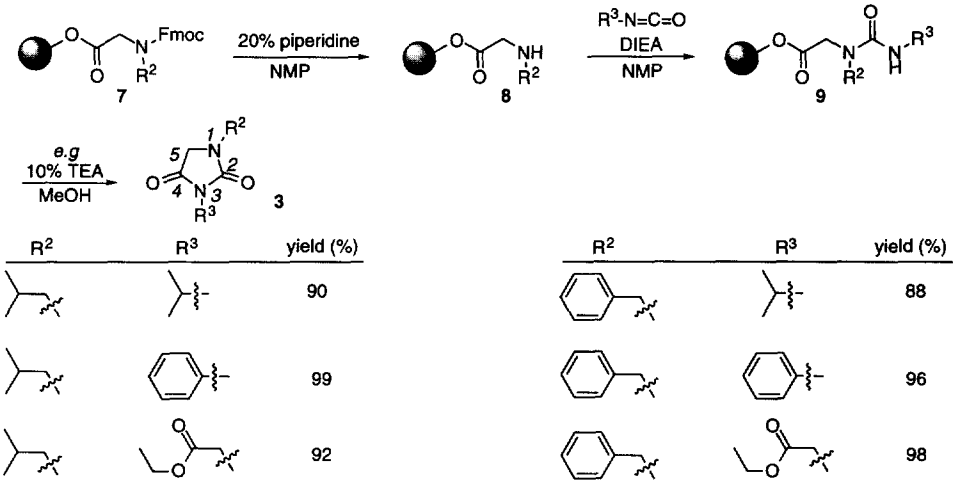
R^1	R^3	yield (%)
H		70*
H		80*
H		99*
H		80*
H		70*
H		91*
H		>99*
		70
		92
		>99
		>99
		40*
		>99
		>99
		80
		>99
		>99
		>99
		64*
		>99
		87

R^1	R^3	yield (%)
		66
		>99
		96
		>99
		50*
		>99
		92
		70
		>99
		>99
		>99
		40*
		>99
		>99
		>99
		>99
		>99
		>99
		48*
		>99
		>99

Scheme 2 (continued). Solid-phase synthesis of 3,5-disubstituted hydantoins starting from amino acids

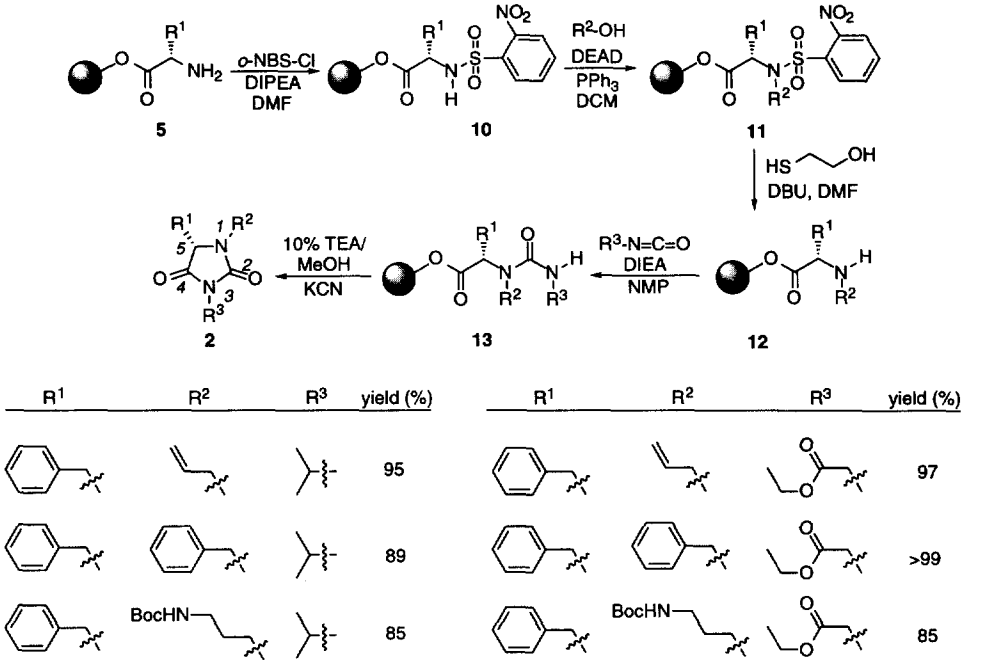
As was more or less expected, reaction of the immobilized amino acids with the extremely sterically hindered adamantyl isocyanate did not result in exclusive formation of the corresponding hydantoins. Due to steric hindrance, mixtures of products were formed instead. An unexpected result however, was that reactions of Tentagel attached glycine with isocyanates did not give complete ring closure either (products marked with "*" in Scheme 2). NMR analysis indicated that the ethyl esters of the linear urea's were formed, either as major or as by-products.[11]

Before moving towards the preparation of 1,3,5-trisubstituted hydantoins **2**, which originate from N-substituted amino acids other than glycine (Scheme 1), a six-member library of 1,3-disubstituted hydantoins **3** was prepared starting from N-substituted glycines also denoted as peptoid monomers.[3] The procedure is quite analogous to the preparation of 3,5-disubstituted hydantoins and is shown in Scheme 3.



Scheme 3. Solid-phase synthesis of 1,3-disubstituted hydantoins starting from peptoid monomers

Having shown (Scheme 3) that hydantoins can also be prepared from N-substituted glycine derivatives, we embarked on the preparation of 1,3,5-trisubstituted hydantoins starting from other N-substituted amino acids. These N-substituted amino acids are now readily accessible by using a procedure developed in our laboratory featuring the use of a Mitsunobu reaction.[4] In this procedure, the N-terminus of the resin-bound amino acid **5** was treated with a solution of *o*-nitrobenzenesulfonylchloride and DIEA in DMF to give the corresponding sulfonamide (Scheme 4). The increased acidity of the sulfonamide N-H in **10** allowed a Mitsunobu reaction with an alcohol to give the N-substituted sulfonamides **11**. Cleavage of the sulfonyl protecting group with mercaptoethanol and reaction of the liberated amines **12** with an isocyanate afforded urea derivatives **13** which were subjected to base-catalyzed cyclization/cleavage and the trisubstituted hydantoins **2**. Using this procedure a six-member library of trisubstituted hydantoins was prepared. Tentagel containing phenylalanine and three different alcohols were used (allyl alcohol, benzyl alcohol and *N*-Boc-aminopropanol), together with two isocyanates (isopropyl isocyanate and ethyl isocyanatoacetate). All products were obtained in excellent yields (85–100%). The structure and identity of all products were confirmed by NMR spectroscopy. The compounds and yields are listed in Scheme 4.



Scheme 4. Solid-phase synthesis of 1,3,5-trisubstituted hydantoins

In conclusion, we have provided access to the combinatorial chemistry of hydantoins by developing convenient and versatile methods for the solid phase synthesis of libraries of 3,5-, 1,3- and 1,3,5-substituted hydantoins. The method also involves an exceptionally mild cyclization/cleavage condition which leads to high yields of the desired compounds. Especially the preparation of trisubstituted hydantoins will enable application of the rigid hydantoin ring as a scaffold to which three pharmacophoric groups can be attached.

Acknowledgment: Financial support for this work was obtained from Solvay Pharmaceuticals. We thank Mr. Mesut Özturk and Ms Lovina Hofmeyer for their assistance in synthesizing the starting peptoid monomers.

References and Notes

1. See e.g.: Gordon, D. W.; Steele, J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 47; Szardenings, A. K.; Burkoth, T. S.; Lu, H. H.; Tien, D. W.; Campbell, D. A. *Tetrahedron* **1997**, *53*, 6573; Scott, B. O.; Siegmund, A. C.; Marlowe, C. K.; Pei, Y.; Spear, K. L. *Molecular Diversity* **1995**, *1*, 125.
2. (a) DeWitt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Reynolds Cody, D. M.; Pavia, M. R. *Proc. Natl. Acad. Sci.* **1993**, *90*, 6909; (b) Dressmann, B. A.; Spangle, L. A.; Kaldor, S. W. *Tetrahedron Lett.* **1996**, *37*, 937; (c) Kim, S. W.; Ahn, S. Y.; Koh, J. S.; Lee, J. H.; Ro, S.; Cho, H. Y. *Tetrahedron Lett.* **1997**, *38*, 4603; (d) Matthews, J.; Rivero, R. A. *J. Org. Chem.* **1997**, *62*, 6090; (e) Sim, M. M.; Ganesan, A. *J. Org. Chem.* **1997**, *62*, 3230; (f) Xiao, X.; Ngu, K.; Chao, C.; Patel, D. V. *J. Org. Chem.* **1997**, *62*, 6968.
3. Kruijtzer, J. A. W.; Liskamp, R. M. J. *Tetrahedron Lett.* **1995**, *36*, 6969; Kruijtzer, J. A. W. Thesis, Utrecht University 1996; Kruijtzer, J. A. W.; Hofmeyer, L. J. F.; Heerma, W.; Versluis C.; Liskamp, R. M. J. *Chem. Eur. J. accepted for publication.*

4. Reichwein, J. F.; Liskamp, R. M. J. *Tetrahedron Lett.* **1998**, *39*, 1243.
5. To our knowledge all reported methods (see ref 2) involve at least *heating* in the presence of base.
6. Boeijen, A.; Liskamp, R. M. J. *manuscript in preparation* .
7. A protected amino acid or peptoid (N-substituted glycine) monomer was esterified to a polyethyleneglycol grafted polystyrene resin (Tentagel® S-OH, 0.30 mmol/g) in a mixed anhydride coupling method employing 2,6-dichlorobenzoyl chloride as was described by Sieber: Sieber, P. *Tetrahedron Lett.* **1987**, *28*, 6147.
8. General procedure for the preparation of a hydantoin: resin bound amino acid **4** or peptoid monomer **7** (500 mg, 0.27 mmol/g) was washed with NMP (3 × 5 mL) and subsequently treated with a solution of 20% piperidine in NMP. Agitation was effected by nitrogen bubbling. After 20 min the solvent was removed by filtration and the resin was washed with NMP (5 × 5 mL). A solution of an isocyanate (0.81 mmol, 6 equivs.) and DIEA (23 μL, 0.14 mmol, 1 equiv) in NMP (2.5 mL) was added. After 3 h, the solvent was removed by filtration. Cyclization/cleavage was effected by addition of a mixture of 10% TEA/MeOH (10 mL) and shaking for 3 h, followed by washing of the resin with MeOH (3 × 5 mL) and DCM (3 × 5 mL). Evaporation of the filtrate and purification by rapid column chromatography (silica, eluent EtOAc) afforded the desired product.
9. The yields are overall yields over four steps (including loading of Tentagel) and are based on a loading of 0.30 mmol.g^{-1} Tentagel® S-OH. The structure and identity of all products were confirmed by ^{1}H and ^{13}C NMR spectroscopy.

   NMR-spectra of a few representative hydantoins: (R_1 = *i*-Bu, R_2 = H, R_3 = CH_2CO_2Et): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, 6H), 1.27 (t, 3H), 1.59 (m, 1H), 1.79 (m, 2H), 4.17 (m, 5H), 6.69 (s, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.0, 21.5, 23.0, 25.0, 39.3, 40.9, 56.1, 61.8, 156.9, 167.0, 174.0 ppm; (R_1 = H, R_2 = CH_2Ph, R_3 = *i*-Pr): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (d, 6H), 3.65 (s, 2H), 4.35 (m, 2H), 4.53 (s, 2H), 7.23–7.37 (m, 5H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 19.6, 44.0, 46.6, 48.8, 128.1, 129.0, 135.5, 169.7 ppm.
10. MULTIBLOCK is distributed by: **CSPS**, P.O. Box 68212, Tuscon, AZ 85737, USA and **SciTech**, Nad Sarkou 75, 160 00 Praha 6, Czech Republic
11. Possibly the increased flexibility of the glycine derivatives is counterproductive for formation of the hydantoin ring.