Base-Promoted Solid-Phase Synthesis of Substituted Hydantoins and Thiohydantoins

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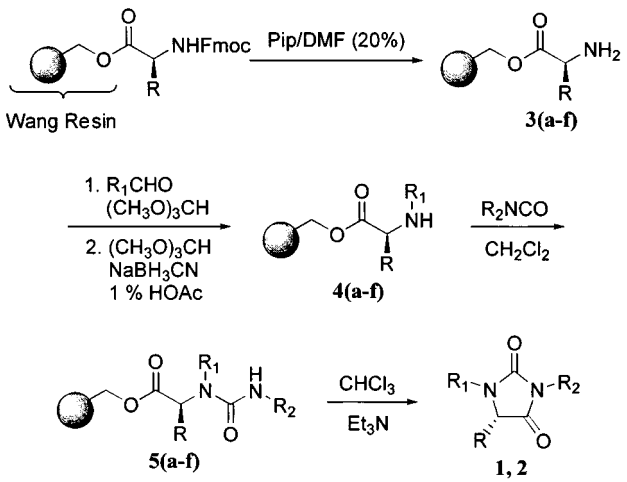
Introduction

Recently, the synthesis of structurally diverse, nonpeptidic compounds by the solid phase approach has received considerable attention.[1] Specifically, the synthesis of small organic molecules which have improved pharmacological properties over peptides has become a major focal point for pharmaceutical companies in search of leads utilizing automated high-throughput biological screening (HTS).

The solid-phase synthesis of heterocycles bearing one or more nitrogen atoms has received much of the attention thus far. Benzodiazepines,[2] diketopiperazines,[3] benzylpiperazine,[4] diazines,[5] and hydantoins[6] are just a few such examples. Hydantoin-based scaffolds which have been previously prepared utilizing standard solution chemistry have been found to possess significant pharmacological activity as central nervous system agents.[7,8]

All previous efforts to prepare the hydantoin scaffold on the solid-phase have focused on the ring synthesis from acyclic precursors.[6] For example, DeWitt[6b] reacted a resin-bound amino acid (linked to the resin through a C-terminal ester functionality) with a variety of substituted isocyanates to generate the urea precursor. The desired products were cyclized and spontaneously cleaved with strong acid at elevated temperatures. This technique, while very effective for generating a diverse set of hydantoins is, however, limited to generating hydantoins with acid-stable functionality. Presumably, acid-sensitive functionality would not survive the cyclization-cleavage conditions. Dressman[6a] addressed this issue by employing a base-promoted cyclization−cleavage sequence to generate the desired hydantoins. In this case, however, the synthesis utilizes only commercially available trisubstituted α-amino acids and primary amines to generate a library of hydantoins. The amino acid building blocks here clearly limit the potential diversity.

Scheme 1



Neither of the aforementioned procedures thoroughly takes advantage of the versatility and wealth of commercially available starting materials; i.e., amino acids, primary amines, and aldehydes. Incorporating each of these starting materials into the necessary sequence of reactions both enhances the molecular diversity of the hydantoin scaffold and the chances of finding a novel "hit" through high throughput screening. Furthermore, the functionality of each reactive group leads to an extremely efficient chemical transformation lending itself to automated synthesis.

Described herein is the solid-phase synthesis of a library of 1,3,5-trisubstituted hydantoins that is characterized by three rapid and efficient steps: (1) Reductive alkylation of a resin-bound α-amino acid with variety of aldehydes; (2) acylation of the secondary amine with an isocyanate to generate a urea precursor; and (3) base-promoted cyclization of the acyclic urea precursor to the hydantoin with concomitant cleavage of the desired compounds cleanly from the resin.

Results and Discussion

The preparation of the hydantoin skeleton is outlined in Scheme 1. Our approach to the synthesis of three-dimensional hydantoins **1** and **2** features a reductive amination step of the primary amine **3** (deprotected in the previous step) of an α-amino acid linked to Wang resin, using variations of previously reported strategies[2a,3a,9] to provide the secondary amine intermediate **4**. For this library, we chose to use three different aldehydes: neutral, electron-rich, and aliphatic, to demonstrate the broad utility of the reductive amination reactions. A negative ninhydrin test indicated completeness of each reaction. Due to the varying electronic nature of each aldehyde, slightly different reaction conditions were incorporated for each aldehyde as optimization of the reactions was essential for library preparation. For each resin-bound intermediate, the structures were verified by cleaving a small sample of resin with 90% TFA/H_2O. Although bis-alkylation to the tertiary amine is a major concern with many literature procedures, we detected only the desired monoalkylated products off of resin **4**.

The acylation of the sterically hindered amine **4** was achieved by reacting the secondary amine with substi-

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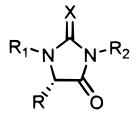
Table 1. Yields of Substituted Hydantoins



prod.	X	R	R_1	R_2	% yield[a]
1a	O	CH_2Ph	CH_2Ph	Ph	58
1b	O	CH_2Ph	CH_2Ph	$(CH_2)_2Ph$	91
1c	O	CH_2Ph	CH_2(3,4,5-$(MeO)_3$Ph)	Ph	64
1d	O	CH_2Ph	CH_2(3,4,5-$(MeO)_3$Ph)	$(CH_2)_2Ph$	56
1e	O	CH_2Ph	$(CH_2)_4CH_3$	Ph	73
1f	O	CH_2Ph	$(CH_2)_4CH_3$	$(CH_2)_2Ph$	48
2a	O	(1*S*)-methylpropyl	CH_2Ph	Ph	56
2b	O	(1*S*)-methylpropyl	CH_2Ph	$(CH_2)_2Ph$	70
2c	O	(1*S*)-methylpropyl	CH_2(3,4,5-$(MeO)_3$Ph)	Ph	69
2d	O	(1*S*)-methylpropyl	CH_2(3,4,5-$(MeO)_3$Ph)	$(CH_2)_2Ph$	54
2e	O	(1*S*)-methylpropyl	$(CH_2)_4CH_3$	Ph	88
2f	O	(1*S*)-methylpropyl	$(CH_2)_4CH_3$	$(CH_2)_2Ph$	50
9	O	CH_2Ph	H	$(CH_2)_2$((3-MeO,4-EtO)Ph)	100
11a	S	CH_2Ph	CH_2Ph	Ph	95
11b	S	CH_2Ph	CH_2(3,4,5-$(MeO)_3$Ph)	Ph	98
11c	S	(1*S*)-methylpropyl	$(CH_2)_4CH_3$	Ph	92

[a] All yields were on crude material. Purity of crude products was >90% by HPLC analysis.

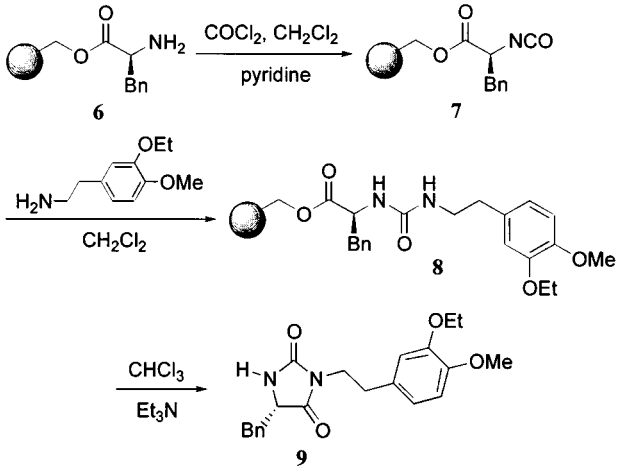
tuted isocyanates (aromatic and aliphatic) overnight at room temperature to provide the acyclic resin-bound precursor **5**. Best results were achieved when a chlorinated solvent (CH_2Cl_2) was utilized. Cleavage of the urea intermediate **5** with 90% TFA/H_2O verified the complete and clean conversion of **4** to **5** in all cases except during formation of **1f**. Since the yield of product **1f** was only 48%, determination of the byproducts which presumably remained on the resin was necessary. Cleavage of resin intermediate **5f** with 90% TFA/H_2O indicated that there was still some urea product on the resin which didn't cleave under the base-promoted cleavage, as determined by MS and LC data. However, more importantly, the results also indicated that mixing the reaction of **4** with phenethyl isocyanate for three days at room temperature still resulted in incomplete acylation of **4** to **5** as determined by LC and MS data.

As demonstrated by Dressman,[6b] base-promoted cyclization of our acyclic intermediates (**5**) accompanied by spontaneous cleavage of the targeted materials from the resin provided hydantoins **1** and **2** in modest to good yields. Analysis of the hydantoin products, shown in Table 1, by HPLC indicated the compounds to be >90% pure. All the yields were based on manufacturers loading, and LC traces obtained were of the isolated, crude material.

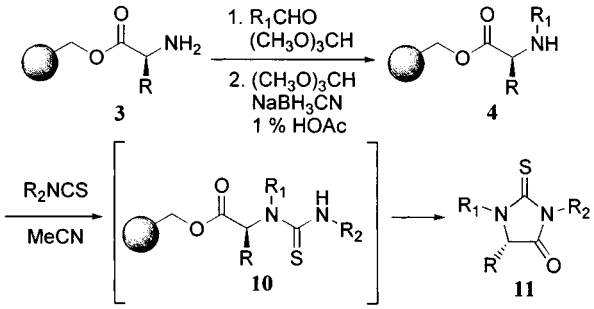
We decided to compare our base-promoted protocol with the DeWitt procedure.[6b] Accordingly, resin-bound intermediate **5c** (where R = benzyl, R_1 = 3,4,5-trimethoxyphenyl, and R_2 = phenyl) was heated at 94 °C for 2 h in 6 N HCl. The requisite product **1c** was formed as per identification by HPLC analysis. However, the yield of **1c** was much lower (16% vs 64%) than the base-promoted reaction.

Alternatively, when developing SAR is the primary focus, a slightly different approach can be taken, as shown in Scheme 2. This approach addresses the issue of how to incorporate functionality not found in commercially available isocyanates. This route takes advantage of the multitude of commercially available primary amines. As demonstrated, resin intermediate **6** is converted to its corresponding isocyanate **7** utilizing excess phosgene and base. A negative ninhydrin test indicates the conversion of **6** to **7**, and the resin-bound isocyanate is then washed several times with DMF and CH_2Cl_2 and used without any further characterization. Reaction of

Scheme 2



Scheme 3



isocyanate **7** with a primary amine generates **8**, the urea intermediate. Ring cyclization and closure in the presence of base generates the desired hydantoin **9** cleanly and in excellent yield. The application of this chemistry opens a new avenue toward the development of diverse two- and three-dimensional libraries.

In contrast to the numerous examples in the literature pertaining to the synthesis of hydantoin scaffolds on solid supports, there are few examples of the synthesis of thiohydantoins.[10] Scheme 3 demonstrates the utility of isothiocyanates when reacted with N-substituted amino

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acids **4** to generate the thiourea intermediates **10**. As previously reported[10a] the thiourea intermediates were found to slowly cyclize upon standing in the absence of base or heating. While this reaction takes place spontaneously at room temperature, optimum yields were obtained when the reactions were heated at reflux in acetonitrile overnight. All attempts to isolate the thiourea precursor failed, making it impossible to wash away excess reagent. The isothiocyanate was therefore used as the limiting reagent to avoid the need to separate the desired product from the isothiocyanate. Alternatively, an excess of reagent could be used and ultimately removed by reaction with a solid-supported "covalent scavenger", such as aminomethylpolystyrene.[11]

While the product hydantoins are optically active, as evidenced by their optical rotations, the enantiomeric purity of the final products will be addressed in a future publication.[12]

Experimental Section

General. The Fmoc-(L)-Phe Wang resin (0.49 mmol/g and 0.87 mmol/g) and the Fmoc-(L)-ILe Wang resin (0.48 mmol/g) were purchased from NovaBiochem. Proton NMR spectra were obtained in CD_3OD and determined with a Bruker AC-300 spectrometer. Chemical shifts are expressed in ppm (δ) with respect to TMS as an internal standard. Electrospray ionization mass spectra (ESI) were obtained using a Fisons spectrometer (Hewlett-Packard HPLC driven electrospray MS instrument). Products were purified by radial chromatography (silica gel) to determine accurate optical rotations, and the purity was determined utilizing a Hewlett-Packard LC system (YMC column, 4 mm × 50 mm, 4 mm C_{18}, 220, 260, and 280 nm; 1.0 mL/min, 3 min gradient from 60% H_20 (0.1% TFA) to 5% H_2O (0.1% TFA)). Optical rotations were obtained on a Perkin Elmer 241 polarimeter.

General Procedure for the Deprotection of the Fmoc-Protected Amino Acids (3a and 3b). To the Fmoc-Wang resins (5.0 g) was added 20% piperidine/DMF solution (35 mL), and the suspension was mixed at room temperature for 30 min. The resin was filtered, washed several times with DMF, MeOH, and CH_2Cl_2, and dried in vacuo overnight.

General Procedure for the Preparation of Hydantoins 1a−f and 2a−f. To the appropriate resin (0.284 mmol), swelled in trimethyl orthoformate (TMOF) (6 mL), was added the appropriate aldehyde (5.68 mmol) and the reaction mixed at room temperature for 30 min. (In the case of 3,4,5-trimethoxybenzaldehyde, it was necessary to mix the resin and aldehyde for 24 h to ensure complete alkylation). $NaCNBH_3$ (5.68 mmol) dispersed in TMOF (3 mL) was added followed by HOAc (0.060 mL), and the reaction was mixed for an additional 10 min. (For valeraldehyde, the reaction was filtered and the resin washed with DMF, CH_2Cl_2, and TMOF (3 × 6 mL each) prior to the addition of $NaCNBH_3$ in TMOF). The reactions were filtered and the resins washed with DMF, MeOH, 10% TEA/DCM, MeOH, DCM, MeOH, and ether. The resins were dried in vacuo to provide intermediate resin **4**. To resin **4** (0.108 mmol), swelled in anhydrous CH_2Cl (2 mL), was added the appropriate isocyanate (1.08 mmol), and the reactions were mixed at room temperature overnight.[13] The resins were filtered and subsequently washed with DMF, MeOH, DCM, MeOH, ether, and dried in vacuo to provide intermediate resin **5**. Resin **5** (0.108 mmol) was reswelled in $CHCl_3$ (1 mL), and triethylamine (1.08 mmol) was added. The reaction was heated at reflux for 24 h and cooled to room temperature, and the solvent was collected. The resin was washed with MeCN and DCM several times, and the washes were combined with the original solvent collected. The combined organic washes were evaporated, and the residue was dried at 50 °C in vacuo to provide a light tan solid. The residues were purified by radial chromatography eluting with hexane/EtOAc (5:1) to provide the desired products as white solids or oils.

1,5-Dibenzyl-3-phenylhydantoin (1a): 22.3 mg (58%); $[\alpha]^{23}_D$ −38.5 (c = 1.01; CD_3OD); HPLC t_R 4.34 min; ^{1}H-NMR (CD_3OD) δ 3.14−3.37 (dd, J = 4 Hz, 2H), 4.31−4.34 (t, J = 4 Hz, 1H), 4.38−4.43 (d, J = 15 Hz, 1H), 5.01−5.06 (d, J = 15 Hz, 1H), 6.94−6.97 (m, 2H), 7.14−7.17 (m, 2H), 7.26−7.41 (m, 10H); ESI MS m/z 357 (M + H^+).

1-(3,4,5-Trimethoxybenzyl)-3-phenethyl-5-(2-butyl)hydantoin (2d): 15.7 mg (54%); $[\alpha]^{23}_D$ −66.8 (c = 0.876; $CDCl_3$); HPLC t_R 4.55 min; ^{1}H-NMR (CD_3OD) δ 0.60−0.62 (d, J = 7 Hz, 3H), 0.84−0.88 (t, J = 7 Hz, 3H), 1.38−1.57 (m, 2H), 1.87−1.91 (m, 1H), 2.88−2.95 (t, J = 7 Hz, 2H), 3.74 (s, 3H), 3.80 (s, 6H), 4.15−4.21 (d, J = 15 Hz, 1H), 4.71−4.76 (d, J = 15 Hz, 1H), 6.58 (s, 2H), 7.14−7.25 (m, 5H); ESI MS m/z 441 (M + H^+).

1-Pentyl-3-phenethyl-5-benzylhydantoin (1f): 21.7 mg (48%); $[\alpha]^{23}_D$ −41.0 (c = 0.967; $CDCl_3$); HPLC t_R 5.03 min; ^{1}H-NMR (CD_3OD) δ 0.88−0.92 (t, J = 7 Hz, 3H), 1.15−1.37 (m, 4H), 1.42−1.54 (m, 3H), 2.43−2.58 (m, 2H), 3.01−3.23 (m, 3H), 3.37−3.52 (m, 2H), 3.55−3.69 (m, 1H), 4.32−4.35 (t, J = 4 Hz, 1H), 7.06−7.28 (m, 10H); ESI MS m/z 365 (M + H^+).

1-(3,4,5-Trimethoxybenzyl)-3-phenyl-5-benzylhydantoin (1c). To intermediate resin **5c** (0.090 mmol) was added 6 N HCl and the reaction heated at 94 °C for 2 h. The reaction was filtered and the resin washed with MeCN and $CHCl_3$. The combined organic washes were evaporated to provide 6.8 mg (16.8%) of crude product after drying.

3-(3-Methoxy-4-ethoxyphenyl)-5-phenylhydantoin (9). To **3a** (515 mg; 0.556 mmol) swelled in DCM (6 mL) was added a phosgene solution in toluene (1.93 M; 1.44 mL; 2.78 mmol) followed by pyridine (0.225 mL; 2.78 mmol), and the reaction was heated at 82 ° C for 1 h. The reaction was filtered, washed with DMF, DCM, and ether, and dried in vacuo to provide intermediate resin **7**. Resin **7** (219 mg; 0.236 mmol) was reswelled in $CHCl_3$ (3 mL), 3-methoxy-4-ethoxyphenethylamine (0.462 mL; 2.36 mmol) was added, and the reaction was mixed at room temperature for 16 h. The resin was filtered, washed with DMF, MeOH, DCM, 10%HOAc/DCM, MeOH, 10% TEA/DCM, MeOH, DCM, MeOH, and ether, and dried in vacuo to provide intermediate resin **8**. Resin **8** (188 mg; 0.164 mmol) was reswelled in $CHCl_3$ (2 mL), triethylamine (0.229 mL; 1.64 mmol) was added, and the reaction was heated at reflux for 72 h. The solvent was collected, and the resin was washed with MeCN and DCM several times. The combined organic washes were evaporated, and the residue was dried in vacuo to provide 60.8 mg (100%) of crude, tan solid. The compound was purified by radial chromatography eluting with hexane/EtOAc (1:5) to provide 19.6 mg (32%) white solid. $[\alpha]^{23}_D$ −46.8 (c = 0.980; $CDCl_3$); HPLC t_R 3.02 min; ^{1}H NMR (CD_3OD): δ 1.39−1.44 (t, J = 6.8 Hz, 3H), 2.45−58 (m, 2H), 2.88−3.10 (dd, 2H), 3.41−3.57 (m, 2H), 4.03−4.10 (q, J = 6.8, 2H), 4.25−4.28 (t, J = 4.5 Hz, 1H), 6.65−6.68 (dd, 1H), 6.74−6.74 (d, 1H), 6.80−6.83 (d, J = 8.1 Hz, 1H), 7.17−7.29 (m, 5H); ESI MS m/z 369 (M + H^+).

General Procedure for the Synthesis of Thiohydantoins 11a−c. To the appropriate resin **4** (0.132 mmol), swelled in 1:1 MeCN/$CHCl_3$ (2 mL), was added phenyl isothiocyanate (0.092 mmol), and the reactions were heated at reflux for 16 h. The reactions were filtered and the resins washed further with MeCN and DCM several times. The combined organic washes were evaporated, and the residues were purified by radial chromatography using hexane/EtOAc (5:1) as the eluent to provide white solids. Yields are based on phenyl isothiocyanate.

1,5-Dibenzyl-3-phenylthiohydantoin (11a): 33 mg (95%); $[\alpha]^{23}_D$ −5.04 (c = 1.01; $CDCl_3$); HPLC t_R 4.70 min; ^{1}H-NMR (CD_3OD) δ 3.13−3.19 (dd, 1H), 3.41−3.51 (dd, 1H), 4.42−4.44 (t, J = 4 Hz, 1H), 4.65−4.70 (d, J = 15 Hz, 1H), 5.82−5.87 (d, J = 15 Hz, 1H), 6.74−6.77 (m, 2H), 7.13−7.27 (m, 2H), 7.29−7.44 (m, 11H); CI MS m/z 373 (M + H^+).

Supporting Information Available: ^{1}H NMR spectra, low-resolution mass spectra, and LC spectra available for all compounds (48 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(12) Also suggestive of the product's configurational integrity was the lack of diastereomer formation for the isoleucine analogs as detected by NMR, TLC, and HPLC. For example, the NMR spectrum of compound **2e** contained a clean doublet at 4.25 ppm for the methine proton of the hydantoin ring.

(13) In the case of **1f**, the reaction of the resin-bound secondary amine with the isocyanate was performed at room temperature for 3 days.