Solution-Phase Synthesis of a Combinatorial Thiohydantoin Library[1]

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An efficient one-pot three-component synthesis of thiohydantoins was developed. In the first step, amino acid esters were alkylated by imine formation with aldehydes and reduction by sodium triacetoxyborohydride. In the second step, an isothiocyanate was added together with a molar equivalent of triethylamine, leading to the thiohydantoin product in high yield and purity after an extractive aqueous workup. This procedure was used to generate a combinatorial library of over 600 discrete thiohydantoins on a 0.1 mmol scale. Sampling of 10% of this library showed the thiohydantoin to be the major product in all cases, with purities of 52−98% by HPLC analysis. The cyclization conditions can also be adapted to the synthesis of hydantoins.

Introduction

In recent years, the combinatorial generation of organic compound libraries has emerged as a powerful tool for drug discovery.[2] Such libraries fall into two general classes: "random" libraries, which can be tested in a variety of biological assays for the identification of novel leads, and "focused" libraries, for lead optimization against a specific target. With random libraries, success depends on the design of a suitable core structure, and one popular approach is to employ heterocycles of proven historical value in the pharmaceutical industry. Such considerations led us to select the hydantoin and thiohydantoin rings as a scaffold. A wide range of properties has been reported for these compounds,[3] including antiviral, antibacterial, antifungal, herbicidal, anticonvulsant, antidiabetic, antiinflammatory, antiulcer, and antiarrhythmic activity.

When we began our work, DeWitt and co-workers at Parke-Davis had reported a hydantoin synthesis[4] as a demonstration of their Diversomer technology (Scheme 1a). Out of 40 parallel reactions, the hydantoin was isolated in 39 cases in 4−81% yield. More recently, two other combinatorial hydantoin syntheses were disclosed. The Lilly group[5] (Scheme 1b) prepared 800 compounds; the hydantoin was detected in 90% of the cases when 15% of the library was sampled. Hanessian and Yang[6] (Scheme 1c) built a library of 50 5-alkoxyhydantoins in solution, with yields averaging 70−90%; the procedure was also adapted to the solid phase.

Results and Discussion

Initially, we were interested in applying the Parke-Davis route (Scheme 1a) to the synthesis of thiohydantoins. In model studies, α-amino acid esters in solution reacted with isothiocyanates to yield thioureas. As expected, these were cyclized to the thiohydantoins by TFA. We then extended the reaction to *N*-alkylamino acid esters, but found that we could not isolate the intermediate thiourea. Instead, the thiohydantoin was formed directly under the conditions (rt, 1 molar equiv of triethylamine) of isothiocyanate addition. For solid-phase synthesis, this was inconvenient, as the ester group was the planned site for resin attachment. When sarcosine bound to Wang resin was reacted with an isothiocyanate, for example, cleaved thiohydantoin product was observed together with excess isothiocyanate in the supernatant. Since large reagent excesses are often used to drive solid-phase reactions to completion, this complicates product purification. A more robust carboxy functional group, for example, an amide[7] instead of an ester, may avoid this problem. However, the ready formation of thiohydantoins suggested an attractive alternative, i.e., to construct a library by conventional solution-phase chemistry.

The synthesis of small-molecule libraries in solution[8] is less popular than the solid-phase methodology, although the former offers advantages such as ease of scale-up and does not require a potentially redundant handle for resin linkage. Furthermore, the vast majority of organic transformations have yet to be optimized for the solid phase. It is likely that the time taken to do so could be equally well spent in developing an effective protocol in solution, especially for short reaction sequences that proceed in high yield. The main advantage of solid-phase synthesis lies in ease of product purification. However, this can often be conveniently accomplished for reactions in solution by liquid−liquid partitioning or the use of scavengers to remove undesired material.[9]

[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1997.

(1) Presented in part at the 2nd Australian Peptide Conference, Fraser Island, Australia, October 6−11, 1996, and the 4th Exploiting Molecular Diversity: Small Molecule Libraries for Drug Discovery, Coronado, CA, February 3−5, 1997.

(2) Many excellent reviews of this area have appeared recently, for example: (a) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2289. (b) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (c) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135.

(3) For reviews, see: (a) López, C. A.; Trigo, G. G. *Adv. Heterocycl. Chem.* **1985**, *38*, 177. (b) Edward, J. T. *Chem. Org. Sulfur Comp.* **1966**, *2*, 287. (c) Ware, E. *Chem. Rev.* **1950**, *46*, 403.

(4) DeWitt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Cody, D. M. R.; Pavia, M. R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 6909.

(5) Dressman, B. A.; Spangle, L. A.; Kaldor, S. W. *Tetrahedron Lett.* **1996**, *37*, 937.

(6) Hanessian, S.; Yang, R.-Y. *Tetrahedron Lett.* **1996**, *37*, 5835.

(7) With an amide, the cyclization would be analogous to the well-known Edman degradation of peptides, which requires acid catalysis.

(8) For representative examples, see: (a) Smith, P. W.; Lai, J. Y. Q.; Whittington, A. R.; Cox, B.; Houston, J. G.; Stylli, C. H.; Banks, M. N.; Tiller, P. R. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2821. (b) Carell, T.; Wintner, E. A.; Sutherland, A. J.; Rebek, J.; Dunayevskiy, Y. M.; Vouros, P. *Chem. Biol.* **1995**, *2*, 171. (c) Pirrung, M. C.; Chen, J. *J. Am. Chem. Soc.* **1995**, *117*, 1240. (d) Storer, R. *Drug Discovery Today* **1996**, *1*, 248.

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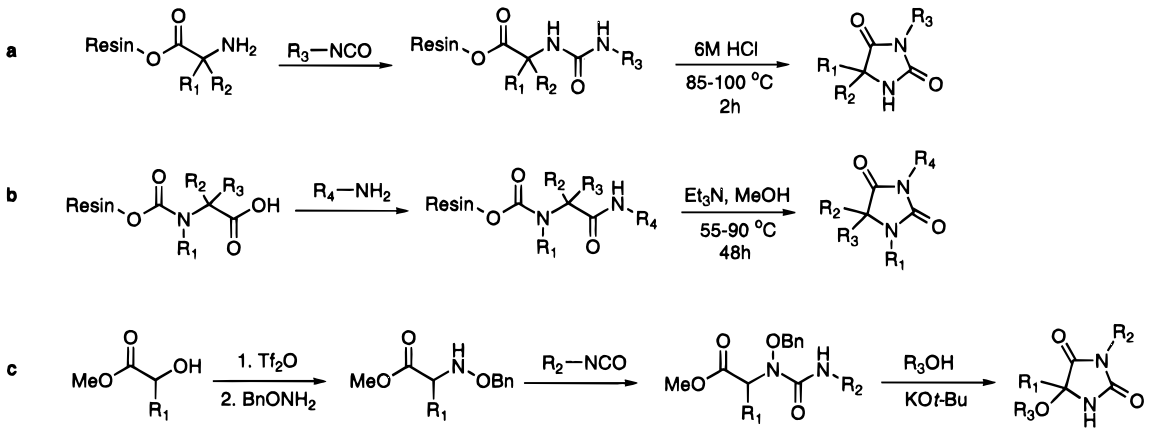
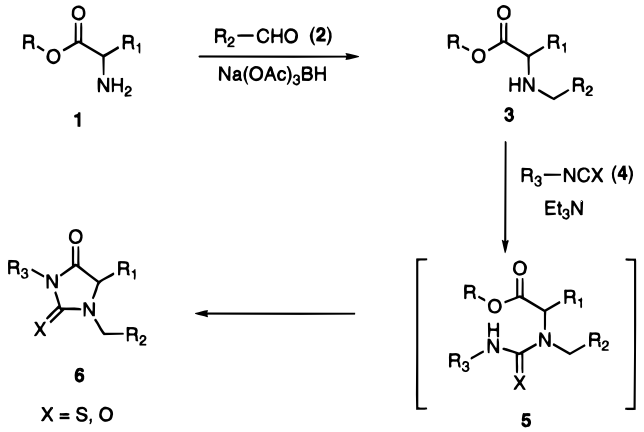
Scheme 1. Combinatorial Syntheses of Hydantoins



Scheme 2. Solution Phase Synthesis of Hydantoins and Thiohydantoins



In our case, further experimentation resulted in an efficient one-pot procedure (Scheme 2, X = S). Our synthesis begins with imine formation between an α-amino acid ester (**1**) and an aldehyde (**2**), followed by *in situ* reduction by sodium triacetoxyborohydride[10] to secondary amine **3**. An isothiocyanate (**4**) is then added to presumably give a thiourea intermediate (**5**) which cyclizes to the thiohydantoin (**6**). This sequence occurs in nearly quantitative yields with stoichiometric reagent quantities. For example, the reaction between L-phenylalanine methyl ester, 2-pyridinecarboxaldehyde, and 4-fluorophenyl isothiocyanate afforded the corresponding thiohydantoin (**7**) in 96% yield after silica gel chromatography.

In the reductive alkylation, aromatic aldehydes gave cleaner reactions than aliphatic examples; electronically deactivated or *ortho*-substituted benzaldehydes required longer reaction times. Consistent with literature observations,[11] sodium triacetoxyborohydride was found to be a better reducing agent than sodium cyanoborohydride. Reductive alkylations with glycine are best terminated once the reaction is complete, to avoid formation of dialkylated product. The final reaction of isothiocyanates with the crude secondary amine was rapid, except with the hindered *tert*-butyl and 1-adamantyl isothiocyanates that gave approximately 10% conversion after 1 h.

Library Synthesis. We have used the above procedure for parallel synthesis of discrete thiohydantoins on a 0.1 mmol scale. Typically, the α-amino acid ester[12] is treated with an aromatic aldehyde in the presence of sodium triacetoxyborohydride, and the reaction monitored by the disappearance of the primary amine using ninhydrin staining. Upon completion, the isothiocyanate is added in the presence of triethylamine. Workup consists of an aqueous wash to remove the borate salts and triethylamine. We have found it advantageous to add glycine as a scavenger prior to workup, as it reacts with excess aldehyde and isothiocyanate to form water-soluble products.

As building blocks, we employed a set of nine α-amino acid esters, 18 aromatic aldehydes, and 19 isothiocyanates (Table 1) to give a potential library of 9 × 18 × 19 (=3078) thiohydantoins. So far, we have made over 600 of these permutations. Approximately 10% of this library was characterized by ^{1}H NMR, HPLC, and MS. Data for selected examples with each building block are shown in Table 2. The mass recovery and purity of these crude thiohydantoins were generally high, considering the simplicity of the workup procedure. We have noticed lower yields with histidine as the amino acid (perhaps due to increased water solubility of the thiohydantoin). In two cases, the recovered mass was slightly over 100%, indicating incomplete removal of starting materials and byproducts. This library has been successfully screened without further purification in a number of bioassays.

Cyclization Studies. We were intrigued by the inability to observe the uncyclized thiourea intermediate (**5**) even with sterically demanding examples despite the mild reaction conditions. In the reaction of primary α-amino acid esters with isocyanates or isothiocyanates, cyclization[13] usually involves heating or acid catalysis. We reinvestigated the reaction between a number of primary α-amino acid esters and isothiocyanates under our conditions and analyzed the products by ^{1}H NMR and MS. Usually, the thiourea was formed (as in our first model studies). In some cases, mixtures of thioureas and thiohydantoins were observed, while only the thiohydantoin was detected in one example. Prolonged treatment

(9) For example, see: (a) Cheng, S.; Tarby, C. M.; Comer, D. D.; Williams, J. P.; Caporale, L. H.; Myers, P. L.; Boger, D. L. *Bioorg. Med. Chem.* **1996**, *4*, 727. (b) Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193. (c) Studer, A.; Hadida, S.; Ferrito, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823.

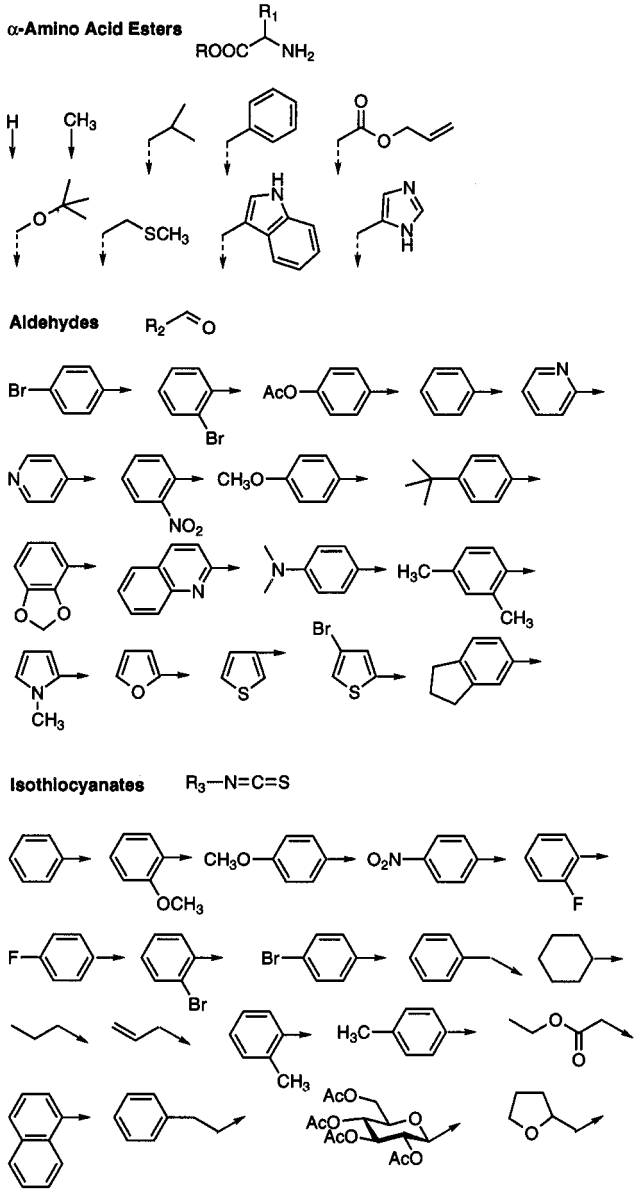
(10) (a) Abdel-Majid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* **1990**, *31*, 5595. (b) Abdel-Majid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

(11) (a) Ramanjulu, J. M.; Joullié, M. M. *Synth. Commun.* **1996**, *26*, 1379. (b) Szardenings, A. K.; Burkoth, T. S.; Look, G. C.; Campbell, D. A. *J. Org. Chem.* **1996**, *61*, 6720.

(12) A molar equivalent of triethylamine is added if the amine is in the form of an acid salt.

(13) (a) Henichart, J. P.; Bernier, J. L. *Synthesis* **1980**, 311. (b) Jacobsen, N.; Toelberg, J. *Synthesis* **1986**, 559. (c) Stella, V.; Higuchi, T. *J. Org. Chem.* **1973**, *38*, 1527.

Table 1. Building Blocks for the Thiohydantoin Library

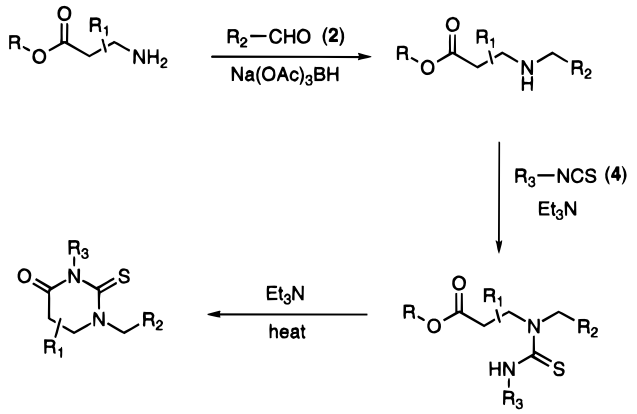


with triethylamine at room temperature uniformly resulted in cyclization, except for a thiourea derived from the hindered serine *tert*-butyl ester. There was no obvious trend correlating the substitution pattern to the cyclization rate.[14]

We wished to determine if these cyclization conditions are suitable for the synthesis of hydantoins (Scheme 2, X = O). Twenty representative examples are shown in Table 3; data for a purified compound (**8**) are included in the Experimental Section. With the aromatic isocyanates, cyclization to the hydantoin occurred under the same conditions as the thiohydantoins (rt, 1 h). The two aliphatic isocyanates tested (propyl, cyclohexyl) typically required longer reaction times (rt, overnight) for complete cyclization.

Finally, we have also explored the homologous 6-membered ring cyclization of β-amino acid esters to 2-thioxo-4-pyrimidinones[15] (Scheme 3). Preliminary studies with β-alanine methyl ester revealed no cyclization of the thiourea with triethylamine at room temperature. Heating the reaction mixture to 80 °C in triethylamine gave varying amounts of cyclized material.[16] Thioureas derived from aliphatic isothiocyanates appear to cyclize faster than their aromatic counterparts, possibly due to the increased basicity at nitrogen.[17] We are presently optimizing general conditions suitable for a variety of β-amino acid esters; data for a compound (**9**) prepared from β-aminohydrocinnamic acid are included in the Experimental Section.

Scheme 3. Solution Phase Synthesis of Thioxopyrimidinones



Summary

We have developed a thiohydantoin synthesis suitable for the generation of combinatorial libraries. All steps occur under mild conditions at room temperature. The products contain three variable substituents, allowing for considerable molecular diversity. The building blocks used—amino acids, aldehydes, and isothiocyanates—are readily available commercially.

Experimental Section

All chemicals were obtained from commercial suppliers and used without further purification. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F_{254}), and spots were visualized with UV light. Column chromatography was performed with silica (Merck, 70−230 mesh). HPLC analysis was performed with a Hewlett-Packard 1040 equipped with a Hypersil ODS C18 reverse-phase column (2.1 × 200 mm). Runs used an acetonitrile:water gradient (70:30 to 100:0 over 35 min, flow rate 0.3 mL/min) with diode-array UV detection at 210 nm. ^{1}H and ^{13}C NMR were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solvent. Chemical shifts are expressed in ppm relative to internal TMS. Infrared spectra (IR) were recorded with a Bio-Rad FTS 165. Low-resolution mass spectra were determined using a Perkin-Elmer Sciex API 3$^+$ or a VG7035, while high-resolution spectra (HRMS) were obtained with a Micromass 7035E.

(*S*)-1-(2-Pyridylmethyl)-3-(4-fluorophenyl)-5-(phenylmethyl)-2-thioxo-4-imidazolidinone (7). To a solution of L-phenylalanine methyl ester hydrochloride (50 mg, 217 μmol) in CH_2Cl_2 (0.5 mL) was added triethylamine (30 μL, 217 μmol), 2-pyridinecarboxaldehyde (21 μL, 224 μmol), and sodium

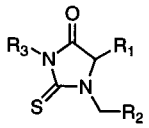
(14) A similar conclusion was reached in the cyclization of peptide isocyanates and isothiocyanates: Nowick, J. S.; Holmes, D. L.; Noronha, G.; Smith, E. M.; Nguyen, T. M.; Huang, S.-L. *J. Org. Chem.* **1996**, *61*, 3929. A valine derivative was partially cyclized at room temperature with triethylammonium hydrochloride: Nomoto, Y.; Takai, H.; Hirata, T.; Teranishi, M.; Ohno, T.; Kubo, K. *Chem. Pharm. Bull.* **1990**, *38*, 3014.

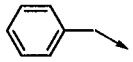
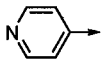
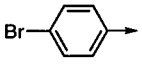
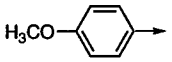
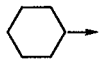
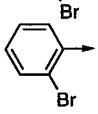
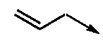
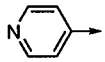
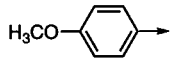
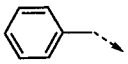
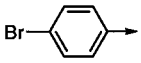
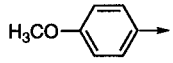
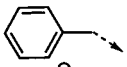
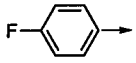
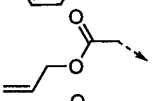
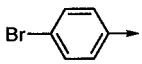
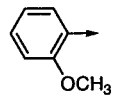
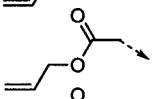
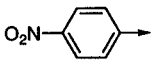
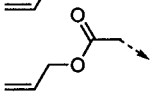
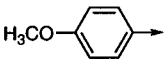
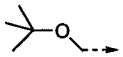
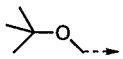
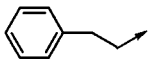
(15) Solid-phase combinatorial approaches to dihydropyrimidine-2,4-diones and quinoxaline-2,4-diones have been reported: (a) Kolodziej, S. A.; Hamper, B. C. *Tetrahedron Lett.* **1996**, *37*, 5277. (b) Buckman, B. O.; Mohan, R. *Tetrahedron Lett.* **1996**, *37*, 4439. (c) Smith, A. L.; Thomson, C. G.; Leeson, P. D. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1483.

(16) These conditions were recently used in a similar cyclization: Hatam, M.; Köpper, S.; Martens, J. *Heterocycles* **1996**, *43*, 1653.

(17) The same trend was observed in ref 15a.

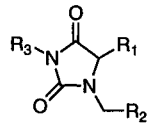
Table 2. Mass Recovery and HPLC Purity of Representative Thiohydantoins

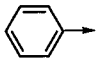
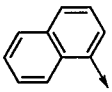
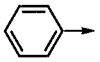
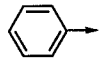
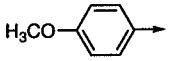
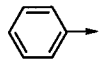
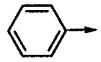
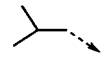
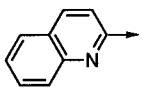
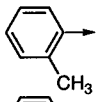
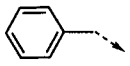
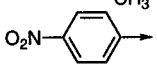
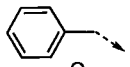
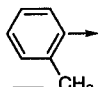
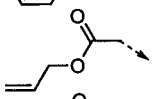
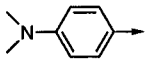
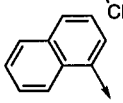
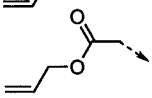
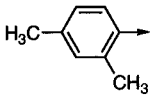
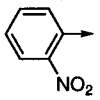
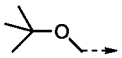
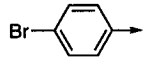
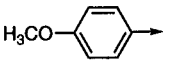
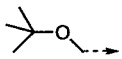
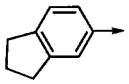
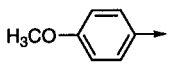
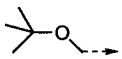
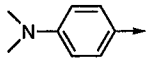
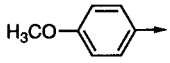


R_1	R_2	R_3	Mass Recovery[a] (%)	HPLC Purity (%)
			85	96
			61	84
			70	83
			79	83
			85	59
			82	57
			87	79
			61	82
			75	87
			105	70
			69	85
			45	72
			74	73
			87	74
			76	86
			75	62
			102	98
			90	85
			55	78
			81	52

[a] Calculated as the ratio of isolated mass over theoretical yield, expressed as a percentage.

Table 3. Mass Recovery and HPLC Purity of Selected Hydantoins



R_1	R_2	R_3	Mass Recovery[a] (%)	HPLC Purity (%)
			105	95
			127	98
			93	89
			89	89
			104	91
			75	45
			102	51
			87	59
			90	78
			88	45
			60	82
			40	57
			47	70
			31	93
			69	82
			93	53
			55	75
			44	66
			80	94
			28	45

[a] Calculated as the ratio of isolated mass over theoretical yield, expressed as a percentage.

triacetoxyborohydride (68 mg, 320 μmol). The reaction mixture was stirred at rt until all the amino acid ester had been consumed as indicated by TLC (1 h). 4-Fluorophenyl isothiocyanate (34 mg, 222 μmol) was then added and the mixture

stirred for 1 h, followed by chromatography on silica gel [hexane:ethyl acetate (75:25 to 0:100)] to yield the thiohydantoin as a low-melting white foam (82 mg, 96%): IR ν_{max} ($CHCl_3$) 1752 cm^{-1}; ^1H NMR δ 3.32 (dd, 1H, J = 3.93, 14.49 Hz, CH_2-Ph), 3.50 (dd, 1H, J = 4.42, 14.46 Hz, CH_2Ph), 4.69 (d, 1H, J = 15.13 Hz, CH_2Py), 4.83 (t, 1H, J = 4.16 Hz, C5-H), 5.89 (d, 1H, J = 15.13 Hz, CH_2Py), 6.74−8.61 (m, 13H, ArH); ^{13}C NMR δ 34.60, 49.78, 63.26, 115.81, 116.11, 123.14, 123.44, 127.71, 128.69, 129.51, 130.01, 130.12, 133.46, 137.04, 149.65, 154.59, 160.84, 164.13, 172.38, 182.74; HRMS calcd for $C_{22}H_{18}FN_3OS$ 391.1155 (M^+), found 391.1160. HPLC purity 83%. Anal. Calcd for $C_{22}H_{18}FN_3OS$: C, 67.33; H, 5.07; N, 11.06; S, 8.02; F, 4.92. Found: C, 67.50; H, 4.63; N 10.73; S, 8.19; F, 4.85.

(*S*)-1-(3-Thienylmethyl)-3-phenyl-5-(3-indolylmethyl)-2,4-imidazolidinedione (8). To a solution of L-tryptophan methyl ester hydrochloride (50 mg, 196 μmol) in CH_2Cl_2 (0.5 mL) was added triethylamine (30 μL, 217 μmol), 3-thiophenecarboxaldehyde (22 μL, 251 μmol), and sodium triacetoxyborohydride (63 mg, 297 μmol). The reaction mixture was stirred at rt for 24 h. Phenyl isocyanate (28 μL, 257 μmol) was then added and the mixture stirred for 1 h, followed by chromatography on silica gel [hexane:ethyl acetate (60:40)] to yield the hydantoin as a white solid (73 mg, 97%): mp 152−153 °C; IR ν_{max} (KBr): 1710 cm^{-1}; ^1H NMR δ 3.40 (dd, 1H, J = 4.42, 15.3 Hz, CH_2Ind), 3.48 (dd, 1H, J = 4.65, 15.25 Hz, CH_2Ind), 4.13 (d, 1H, J = 15.19 Hz, CH_2Th), 4.24 (t, 1H, J = 4.53 Hz, C5-H), 5.06 (d, 1H, J = 15.16 Hz, CH_2Th), 6.88−8.29 (m, 14H, ArH); ^{13}C NMR δ 25.49, 39.96, 58.80, 108.24, 111.33, 118.77, 119.84, 122.34, 123.25, 123.96, 126.07, 127.04, 127.13, 127.48, 128.07, 128.90, 131.52, 136.00, 136.08, 155.66, 171.90; HRMS calcd for $C_{23}H_{19}N_3O_2S$ 401.1198 (M^+), found 401.1184; HPLC purity 97%. Anal. Calcd for $C_{23}H_{19}N_3O_2S$: C, 68.81; H, 4.77; N, 10.47; S, 7.99. Found: C, 68.17; H, 4.99; N 10.63; S, 8.05.

1-(2-Pyridylmethyl)-3,6-(diphenyl)-tetrahydro-2-thioxo-4(3*H*)-pyrimidinone (9). To a solution of DL-3-amino-3-phenylpropionic acid methyl ester (49 mg, 227 μmol) in CH_2Cl_2 (0.5 mL) was added triethylamine (100 μL, 684 μmol), 2-pyridinecarboxaldehyde (32 μL, 336 μmol), and sodium triacetoxyborohydride (87 mg, 410 μmol). The reaction mixture was stirred at rt until all the amino acid ester had been consumed. 4-Bromophenyl isothiocyanate (58 mg, 271 μmol) was then added and the mixture stirred for 1 h, followed by addition of triethylamine (200 μL) and heating at 80 °C for 2 days. The reaction mixture was cooled to rt, diluted with CH_2Cl_2, washed with water, dried over $MgSO_4$, and chromatographed on silica gel [hexane:ethyl acetate (50:50)] to yield the thioxopyrimidinone as a pale yellow foam (75 mg, 73%): mp 68−75 °C; IR ν_{max} (KBr) 1717 cm^{-1}; ^1H NMR δ 3.14 (dd, 1H, J = 1.88, 16.18 Hz, C5-H_2), 3.57 (dd, 1H, J = 6.95, 16.21 Hz, C5-H_2), 4.49 (d, 1H, J = 15.17 Hz, CH_2Py), 5.45−5.51 (br d, 1H, J = 6 Hz, C6-H), 6.26 (d, 1H, J = 15.17 Hz, CH_2Py), 7.22−8.59 (m, 13H, ArH); ^{13}C NMR δ 38.61, 58.41, 58.89, 122.29, 122.94, 123.35, 125.57, 128.66, 129.38, 130.85, 132.12, 136.39, 136.83, 138.31, 149.52, 155.20, 165.10, 181.44; HRMS calcd for $C_{22}H_{18}BrN_3OS$ 451.0354 (M^+), found 451.0349; HPLC purity 95%.

General Procedure for Library Synthesis. A solution of α-amino acid ester in the form of an acid salt (2 mmol), triethylamine (1.1 molar equiv), aldehyde (1.1 molar equiv), and sodium triacetoxyborohydride (1.5 molar equiv) in CH_2Cl_2 was stirred overnight at rt and then quenched with water. The organic phase was washed with water (2×) and dried over $MgSO_4$, and aliquots (each containing 0.1 mmol of secondary amine based on theoretical yield) were distributed into 1.5 mL vials. Triethylamine (14 μL, 0.1 mmol) and isothiocyanate (0.11 mmol) were added into each vial, and the solution was shaken for 1 h. Glycine (1 mmol) was added and the mixture shaken vigorously for 2 h, followed by addition of water and further shaking for 1 h. After separation, the organic phase was washed with water (1.5 mL) and finally evaporated to yield the crude thiohydantoin.

Acknowledgment. We are grateful to attachment students from Ngee Ann and Singapore Polytechnic for assistance with library synthesis and HPLC analysis and the Central Facility Laboratory, Department of Chemistry, and the Centre for Natural Product Research of the National University of Singapore for micronanalysis, NMR, IR, and MS data. This work was supported by grants from the National Science and Technology Board of Singapore.

Supporting Information Available: Characterization (^1H NMR, HPLC, MS) for the crude thiohydantoins in Table 2; ^1H and ^{13}C NMR spectra for compounds **7-9** (46 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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