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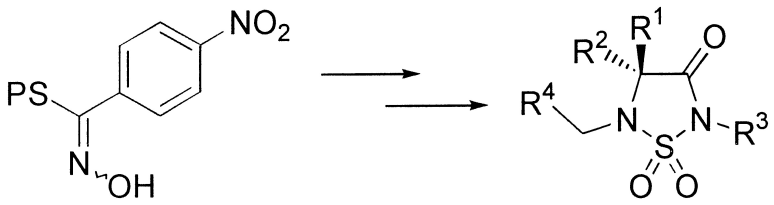

Oxime Resin

28 examples

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Efficient Solid-Phase Synthesis of Sulfahydantoins

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A novel solid-phase strategy allows the efficient preparation of "traceless" sulfahydantoins. A total of 28 derivatives, with crude purity generally higher than 85%, were prepared by parallel synthesis. Through reductive alkylations, Mitsunobu reactions, and sulfamoylation reactions on oxime resin, the synthetic strategy affords sulfahydantoin derivatives selectively substituted at N^2, N^5 and N^2, N^5 positions, although yields of disubstituted compounds are lower. The mild reaction conditions involved lead to sulfahydantoins without racemization.

Solid-phase organic synthesis of heterocycles plays an increasing role in modern drug discovery.[1,2] Heterocycles provide scaffolds onto which pharmacophores can be arranged to yield potent and selective drugs. For example, considerable effort has been invested in the synthesis of hydantoin derivatives. Compounds with this structural motif found applications as agrochemicals[3,4] and therapeutics.[5,6] Sulfahydantoins are analogues of hydantoins and provide heterocyclic scaffolds with a great potential for the construction of bioactive compounds (Figure 1). Indeed, sulfahydantoins have been shown recently to be serine protease inhibitors[7−14] and are investigated as antihypertensives,[15] artificial sweeteners,[16] and histamine H_2 receptor antagonists[17] and for their affinity for MHC class II proteins.[18]

Despite their potential as druglike compounds, the solid-phase synthesis of sulfahydantoins has only been explored scarcely and very recently.[19,20] One of the reasons for this is the harsh conditions required for the cyclization step.[21] Hence, we sought to develop an efficient, mild, solid-phase synthetic strategy that would allow the preparation of a large number of sulfahydantoin analogues selectively substituted at N^2 and N^5 positions. On the basis of our previous work,[21] we report herein such a convenient method that takes advantage of the oxime resin (Scheme 1) as solid support.

Results and Discussion

The oxime resin was chosen as solid support.[22] Cleavage of compounds from this resin is readily achieved under mild nucleophilic conditions.[23] We wanted to exploit this feature to prepare "traceless" sulfahydantoin derivatives by a cyclization/cleavage step. The synthetic strategy for the synthesis of unsubstituted and N^2-substituted sulfahydantoins is illustrated in Scheme 1. The coupling of BOC-protected amino acids to the resin was done under standard conditions using DCC or DIC in a mixture of CH_2Cl_2 and DMF.

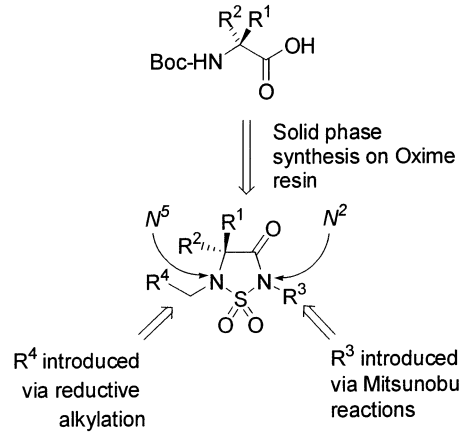

Figure 1. Retrosynthetic scheme and general structure of sulfahydantoins synthesized herein, illustrating the great diversity (R^1−R^4) of pharmacophores that can be oriented by the heterocyclic scaffold.

Sulfamides **2** were obtained using *N*-BOC-protected chlorosulfonamide prepared in situ from chlorosulfonyl isocyanate (CSI) and *tert*-butyl alcohol following a procedure reported by our group.[24] *N*-BOC chlorosulfamide reacts cleanly with the free amino group from an amino acid under basic conditions to give *N*-BOC sulfamide analogues **2**. After deprotection with TFA, the cyclization to afford unsubstituted sulfahydantoins **3** was achieved in good yields using an excess of triethylamine in anhydrous dichloromethane for 3 h at room temperature. All heterocycles **3** were obtained with excellent crude purity, ranging from 89% to higher than 95%. The results are listed in Table 1.

To functionalize N^2 selectively, we attempted Mitsunobu reactions on the BOC-protected sulfonamide **2**. The BOC group increases the acidity of the N^2 proton and allows selective and clean Mitsunobu reactions at this position. Utilization of an excess of reagents during the reaction however gives secondary products mainly due to double alkylation at both N^2 and N^5. Nevertheless, the use of a stoichiometric amount of alcohol yields clean monoalkylation products. All cyclizations were achieved after the deprotec-

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Scheme 1

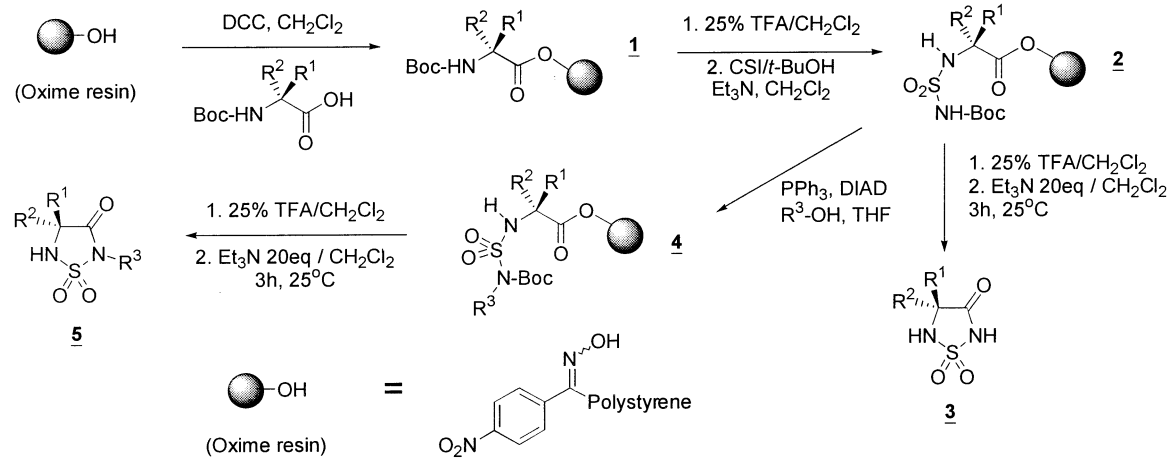


Table 1. Yields and Purity of Crude Sulfahydantoins

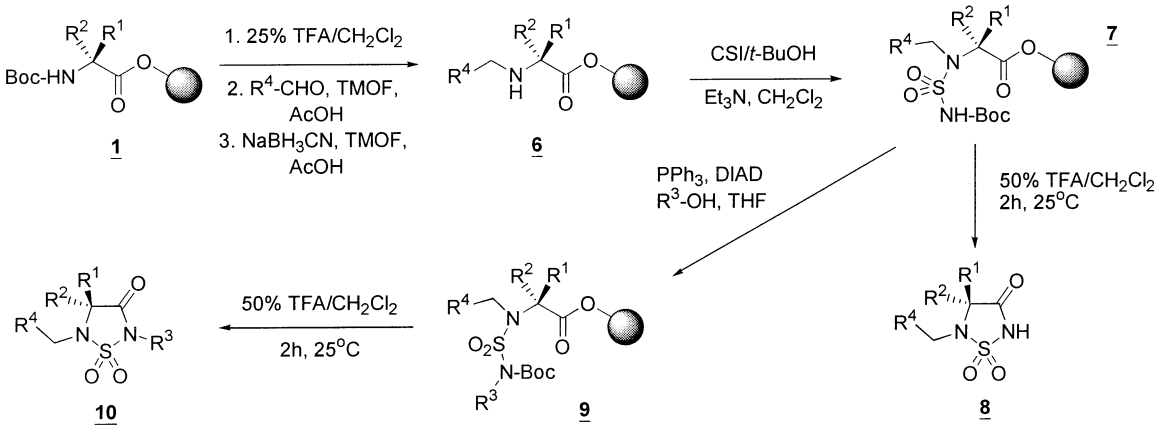
compd	Xaa related to R^1 and R^2	R^3	R^4	% yield, % purity (crude)
3a	L-Phe	H	H	89, >95
3b	L-Val	H	H	57, 89
3c	L-Lys	H	H	56, >95
3d	L-Glu	H	H	52, >95
3e	L-Ser	H	H	62, >95
5a	L-Phe	$-CH_2-CH=CH_2$	H	77, 88
5b	L-Phe	$-CH_2-CH_2-Cl$	H	72, 86
5c	L-Val	$-CH_2-CH_2-$(4-MeOPh)	H	50, >95
5d	L-Val	$-CH_2-Ph$	H	21, >95
5e	L-Val	$-CH_2-CH=CH_2$	H	62, 80
5f	L-Val	$-CH_2-CH_2-Cl$	H	75, 70
5g	L-Val	$-CH_2-CH_2-CH_2-Ph$	H	20, >95
5h	L-Val	$-CH_2-CH_2-CH_2-CH_3$	H	52, 67
5i	L-Val	$-C_6H_{10}$	H	
5j	L-Lys	$-CH_2-CH=CH_2$	H	77, >95
5k	L-Lys	$-CH_2-CH_2-Cl$	H	72, 60
5l	L-Lys	$-CH_2-CH_2-$(4−MeOPh)	H	40, >95
5m	L-Glu	$-CH_2-CH_2-Cl$	H	57, 92
5n	L-Glu	$-CH_2-CH=CH_2$	H	50, 68
5o	L-Glu	$-CH_2-CH_2-$(4-MeOPh)	H	21, >95
5p	L-Glu	$-CH_2-CH_2-CH_2-CH_3$	H	62, >95
5q	L-Ser	$-CH_2-CH=CH_2$	H	50, >95
8a	L-Phe	H	(4-CN)Ph−	72, 82
8b	L-Phe	H	(4-OMe)Ph−	37, 75
8c	L-Phe	H	(4-NO_2)Ph−	55, 85
8d	L-Phe	H	(4-Me)Ph−	43, >95
10a	L-Phe	$-CH_2-CH=CH_2$	(4-Me)Ph−	32, 70
10b	L-Phe	$-CH_2-CH2-CH_2-CH_3$	(4-Me)Ph−	33, 53
10c	L-Phe	$-CH_2-CH_2-CH_2-Ph$	(4-Me)Ph−	26, 62

tion of sulfonamide with TFA, using the same mild nucleophilic conditions as for **3** to give selectively substituted sulfahydantoins **5** (Table 1). Mitsunobu reactions with secondary alcohols gave very low yields and complicated mixtures, most probably because of steric hindrance.

Our approach to the synthesis of N^5-substituted sulfahydantoins **8** on solid support relies on a reductive alkylation step of the deprotected amino acid linked to the oxime resin. For this purpose, we adapted conditions from previously reported protocols.[25] The synthesis of **8** and **10** is shown in Scheme 2. During the deprotection of **7** with TFA, we observed the presence of desired N^5-alkylated sulfahydantoins **8** in the filtrate. It appears that cyclization of deprotected sulfamides **7** occurred more easily than with deprotected sulfamides **2** and **4**. Hence, in the case of N^5-substituted precursors, it is possible to deprotect, cyclize, and cleave in one step to obtain N^5-substituted sulfahydantoins **8** in yields ranging from 37% to 72% and with good (75%) to excellent (> 95%) crude purity (see Table 1).

To extend the scope of our strategy, the sulfamide **7** was reacted with PPh_3 (3.0 equiv), DIAD (3.0 equiv), and various primary alcohols in THF to afford, after deprotection/cyclization with TFA, selectively N^2,N^5-disubstituted sulfahydantoins **10** (Scheme 2). Although the crude nonoptimized yields in these cases are modest (26−33%), the crude purity are good to excellent for these highly substituted heterocycles. We are currently optimizing the conditions to improve the yields. In general, crude products from acid-catalyzed cyclization have very good purity and are obtained by simple evaporation. Compounds **5** are filtered through a short silica

Scheme 2



gel column before evaporation in order to remove minor side products (generally unsubtituted sulfahydantoin) and an excess of triethylamine.

It is noteworthy that the polystyrene bead size affects the ease of cyclization. Indeed, we have found that compounds **4** can be cyclized quite efficiently under acid conditions during TFA cleavage of the BOC group on resin of 100−200 mesh size. Comparatively, cyclization of these compounds on 200−400 mesh resin does not occur under acid conditions and necessitates basic conditions (NEt_3 in CH_2Cl_2). For the less reactive compounds **2**, cyclization is effected only under basic conditions, regardless of mesh size.

The mild conditions used throughout the synthesis should lead to sulfahydantoins with preserved stereochemical integrity. This is supported by the determination of enantiomeric purity of sulfahydantoins by ^{1}H NMR after derivatization on N^5 with (*R*)-(+)-methylbenzyl isocyanate, and the absence of diagnostic peaks from the opposite diastereomer confirmed that the entire sequence minimizes racemization in the final heterocyclic compounds.

Conclusions

The solid-phase synthesis of sulfahydantoins presented here represents a facile route to highly and selectively substituted useful heterocyclic compounds. The key advantages of our strategy include the ability to derivatize selectively the heterocycle scaffold with a huge variety of substituents, the simplicity and rapidity of the whole processes, the efficient "traceless" cyclization cleavage that limits racemization, and the very good purity of crude products. Furthermore, our results constitute the first report of successful Mitsunobu reactions and reductive alkylations on the oxime resin. Future efforts will focus on optimizing reaction yields and on the preparation and screening of libraries of these highly substituted heterocyclic compounds.

Experimental Section

Oxime resin was prepared according to a reported procedure using polystyrene beads (100−200 and 300−400 mesh 1% DVB, Advanced ChemTech, Louiville, KY). Resins with substitution levels of around 0.6 mmol of oxime group per gram were used. BOC-protected amino acids were purchased from Advanced ChemTech. All other reagents were purchased from Sigma Aldrich Co. (Milwaukee, WI). Dichloromethane was distilled from CaH_2, and tetrahydrofuran was distilled from sodium benzophenone. DIEA and triethylamine were distilled from KOH under N_2. Coupling of the first amino acid was performed manually using a peptide solid-phase reaction vessel equipped with a coarse glass frit (Chem Glass, Vineland, NJ). Solid-phase synthesis of sulfahydantoins was performed on a Quest 210 parallel synthesizer from Argonaut Technologies (San Carlos, CA). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz spectrometer. Chemical shifts are reported in ppm relative to deuterated solvents' residual peaks. Mass spectra were recorded on ZAB-IF VG (Université de Sherbrooke) using electronic impact and chemical ionization. HPLC analyses were performed on a Hewlett-Packard 1050 system using a C_5 reverse-phase column (Phenomenex, Torrance, CA) with a gradient of 10% acetonitrile/water containing 0.1% TFA to 100% acetonitrile over 45 min at 1.0 mL/min flow rate.

Typical Procedure for the Coupling of the First Amino Acid. The amino acid (15 mmol) was activated with DCC (15 mmol) during 30 min at 0 °C in CH_2Cl_2, and then it was added to the oxime resin (5 g, 0.6 mmol/g, 3 mmol) swollen in DMF. The mixture was shaken mechanically for 24 h at room temperature. The resin was filtered and washed thoroughly with DMF (3 × 50 mL), MeOH (3 × 50 mL), DMF (3 × 50 mL), and MeOH (3 × 50 mL) and then was dried in vacuo. The amount of coupled amino acid was measured quantitatively by cleavage with *n*-propylamine.[12] Typical loadings of amino acids were around 0.6 mmol/g.

***N*-Sulfamoylation.** BOC-amino acid resins (0.5 g, 0.3 mmol) were transferred into Quest tubes (10 mL), and deprotection was accomplished with 25% TFA in CH_2Cl_2 (30 min), followed by washing with DMF (3 × 8 mL), MeOH (3 × 8 mL), and CH_2Cl_2 (4 × 8 mL). Under N_2, the resulting resins were swollen in anhydrous CH_2Cl_2 (8 mL), and DIEA (0.21 mL, 1.2 mmol) was added to each tube. Simultaneously, a solution of *tert*-butyl chlorosulfonylcarbamate was prepared by addition of *tert*-butyl alcohol (0.8 mL, 8.37 mmol) in CH_2Cl_2 (4 mL) to an ice-cold solution of chlorosulfonyl isocyanate (0.71 mL, 8.1 mmol) in CH_2Cl_2 (5 mL). An amount of 1 mL of the solution was added to each tube, and mixtures were agitated for 1 h. Resins were

filtered and washed with DMF (3 × 8 mL), MeOH (3 × 8 mL), and CH_2Cl_2 (3 × 8 mL).

Preparation of Unsubstituted Sulfahydantoins 3. Resins (0.5 g, 0.3 mmol) were deprotected with 25% TFA in CH_2Cl_2 for 30 min, then washed with DMF (3 × 8 mL), MeOH (3 × 8 mL), and anhydrous CH_2Cl_2 (3 × 8 mL). To the resulting resins swollen in anhydrous CH_2Cl_2, NEt_3 (0.84 mL, 6 mmol) was added, and the mixtures were shaken for 3 h under N_2. Resins were filtered and rinsed with CH_2Cl_2 (2 × 8 mL) directly in empty Quest tubes. The combined organic solutions were washed automatically with a 1 N HCl solution (2 × 10 mL) and water (10 mL). Drying with $MgSO_4$ and evaporation gave the desired sulfahydantoins **3**. The crude purity was assessed by HPLC.

Salient Spectroscopic Data for Derivatives of 3. 4*S*-Benzyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 3a. ^{1}H NMR (DMSO-d_6), δ: 8.25 (br s, 1H); 7.35−7.24 (m, 5H); 4.44 (dd, 1H, $J = 3$ and $J = 10$); 3.14 (dd, 1H, $J = 3$ and $J = 14$); 2.86 (dd, 1H, $J = 10$ and $J = 14$). ^{13}C NMR, δ: 171.4; 136.8; 129.4; 128.3; 126.7; 62.3; 36.7. Exact mass (EI): 226.0415; calcd 226.0412.

4*S*-Isopropyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 3b. ^{1}H NMR (DMSO-d_6), δ: 6.00 (br s, 1H); 5.21 (br s, 1H); 4.19 (d, 1H, $J = 4$); 2.40−2.29 (m, 2H); 1.08 (d, 3H, $J = 7$); 1.03 (d, 3H, $J = 7$). ^{13}C NMR, δ: 170.7; 66.4; 29.8; 19.0; 16.3. Exact mass (CI): MH^+ 179.0487; calcd 179.0490.

4*S*-(Benzyl-4-butylcarbamate)-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 3c. ^{1}H NMR (DMSO-d_6), δ: 6.00 (br s, 1H); 5.21 (br s, 1H); 4.19 (d, 1H, $J = 4$); 2.40−2.29 (m, 2H); 1.08 (d, 3H, $J = 7$); 1.03 (d, 3H, $J = 7$). ^{13}C NMR, δ: 172.2; 156.2; 136.6; 128.0; 127.5; 127.4; 65.5; 61.5; 45.6; 29.5; 28.6; 22.2. Exact mass (EI): 341.1052; calcd 341.1045.

4*S*-(Phenylmethoxycarbonyl)ethyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 3d. ^{1}H NMR (DMSO-d_6), δ: 7.34 (s, 5H); 6.22 (d, 1H, $J = 5$); 5.20 (br s, 1H); 5.12 (s, 2H); 4.33−4.28 (m, 1H); 2.59 (t, 2H, $J = 7$); 2.31−2.09 (m, 2H). ^{13}C NMR, δ: 173.4; 171.0; 135.4; 128.7; 128.4; 128.4; 67.1; 61.1; 30.3; 26.3. Exact mass (EI): 298.0619; calcd 298.0623.

4*S*-(Benzyloxy)methyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 3e. ^{1}H NMR (300 MHz, DMSO-d_6), δ: 7.95−7.6 (br s, 1H); 7.38−7.26 (m, 5H); 4.57 (d, 2H, $J = 2$); 4.29−4.25 (m, 1H); 3.96 (dd, 1H, $J = 3$ and $J = 10$); 3.73 (dd, 1H, $J = 3$ and $J = 10$).

Synthesis of N^2-Substituted Sulfahydantoins 5. After the *N*-sulfamoylation of amino acids described above, resins were washed with THF (3 × 8 mL) and swollen in THF (7 mL). Then PPh_3 (0.3 mmol, 0.3 mL of 1.0 M solution in THF), an alcohol (0.3 mmol), and DIAD (0.06 mL, 0.3 mmol) were added consecutively under N_2. The mixtures were stirred for 1 h and then filtered and washed with DMF (3 × 8 mL), MeOH (3 × 8 mL), and anhydrous CH_2Cl_2 (3 × 8 mL). Cyclizations/cleavages were done as described above. Resins were filtered and washed with CH_2Cl_2 (2 × 8 mL). The combined organic phases were directly filtered on a short silica gel column (around 1.2 g of silica gel in a 10 mL syringe), and the solvent was evaporated to yield the desired N^2-substituted sulfahydantoins **5**.

Salient Spectroscopic Data for Derivatives of 5. 2-Allyl-4*S*-benzyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 5a. ^{1}H NMR ($CDCl_3$), δ: 7.40−7.20 (m, 5H); 5.95−5.75 (m, 1H); 5.40−5.25 (m, 2H); 4.90 (br s, 1H); 4.40 (dd, 1H, $J = 4$ and $J = 8$); 4.20 (dt, 2H, $J = 6$ and $J = 1$); 3.31 (dd, 1H, $J = 4$ and $J = 14$); 3.14 (dd, 1H, $J = 9$ and $J = 14$). ^{13}C NMR, δ: 167.7; 135.0; 129.9; 129.5; 127.7; 129.0; 120.0; 61.7; 43.2; 39.9. Exact mass (EI): 266.0717; calcd 266.0725.

2-Chloroethyl-4*S*-benzyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 5b. ^{1}H NMR ($CDCl_3$), δ: 7.32−7.14 (m, 5H); 4.79 (d, 1H, $J = 7$); 4.37−4.28 (m, 1H); 3.87−3.81 (m, 2H); 3.63 (t, 2H, $J = 7$); 3.20 (dd, 1H, $J = 4$ and $J = 14$); 3.11 (dd, 1H, $J = 8$ and $J = 14$). ^{13}C NMR, δ: 167.7; 134.1; 129.4; 129.2; 128.0; 61.5; 41.9; 39.6; 36.5. Exact mass (EI): 288.0331; calcd 288.0335.

2-(4-Methoxyphenethyl)-4*S*-isopropyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 5c. ^{1}H NMR ($CDCl_3$), δ: 7.17 and 6.83 (2d, 4H, $J = 9$); 4.97 (d, 1H, $J = 7$); 4.07 (dd, 1H, $J = 4$ and $J = 7$); 3.88−3.70 (m, 2H); 3.78 (s, 3H); 2.98 (t, 2H, $J = 8$); 2.38−2.34 (m, 1H); 1.05 (d, 3H, $J = 7$); 0.90 (d, 3H, $J = 7$). MS (ESI, negative ion): 311 $(M - 1)^-$; calcd 312.11.

2-Benzyl-4*S*-isopropyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 5d. ^{1}H NMR ($CDCl_3$), δ: 7.43−7.31 (m, 5H); 5.03 (d, 1H, $J = 7$); 4.72 (s, 2H); 4.10 (dd, 1H, $J = 4$ and $J = 6$); 2.40−2.30 (m, 1H); 1.04 (d, 3H, $J = 7$); 0.90 (d, 3H, $J = 7$). MS (ESI, negative ion): 267 $(M - 1)^-$; calcd 268.09.

2-Allyl-4*S*-isopropyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 5e. ^{1}H NMR ($CDCl_3$), δ: 5.95−5.80 (m, 1H); 5.42−5.28 (m, 2H); 5.05 (br s, 1H); 4.20 (d, 2H, $J = 6$); 4.13 (d, 1H, $J = 4$); 2.42−2.32 (m, 1H); 1.07 (d, 3H, $J = 7$); 0.97 (d, 3H, $J = 7$). ^{13}C NMR, δ: 167.0; 129.8; 120.0; 66.0; 42.9; 30.2; 18.9; 16.3. Exact mass (EI): 218.0728; calcd 218.0725.

2-Chloroethyl-4*S*-isopropyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 5f. ^{1}H NMR ($CDCl_3$), δ: 4.17 (d, 1H, $J = 4$); 3.98−3.91 (m, 2H); 3.75 (br s, 1H); 3.76 (t, 2H, $J = 7$); 2.43−2.35 (m, 1H); 1.08 (d, 3H, $J = 7$); 1.00 (d, 3H, $J = 7$). ^{13}C NMR, δ: 167.2; 66.2; 41.7; 39.6; 30.1; 18.9; 16.4. Exact mass (CI), MNH_4^+: 258.0674; calcd 258.0679.

2-(3-Phenylpropyl)-4*S*-isopropyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 5g. ^{1}H NMR ($CDCl_3$), δ: 7.32−7.18 (m, 5H); 4.85 (br s, 1H); 4.11 (d, 1H, $J = 4$); 3.65 (t, 2H, $J = 7$); 2.69 (t, 2H, $J = 8$); 2.41−2.33 (m, 1H); 2.09 (q, 2H); 1.07 (d, 3H, $J = 7$); 0.98 (d, 3H, $J = 7$). ^{13}C NMR, δ: 167.3; 140.4; 128.4; 128.2; 126.1; 65.9; 40.7; 32.8; 30.1; 29.2; 18.9; 16.3. Exact mass (EI): 296.1200; calcd 296.1195.

2-Butyl-4*S*-isopropyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 5h. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 5.14 (br s, 1H); 4.12 (d, 1H, $J = 3$); 3.59 (dd, 2H, $J = 7$ and $J = 8$); 2.40−2.30 (m, 1H); 1.76−1.66 (q, 2H); 1.43−1.31 (m, 2H); 1.06 (d, 3H, $J = 7$); 0.96 (d, 3H, $J = 7$); 0.94 (t, 3H, $J = 7$). MS (ESI, negative ion): 233 $(M - 1)^-$; calcd 234.12.

2-Allyl-4*S*-(benzyl-4-butylcarbamate)-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 5j. ^{1}H NMR ($CDCl_3$), δ: 7.38−7.30 (m, 5H); 6.15 (br s, 1H); 5.95−5.8 (m, 1H); 5.40−5.26 (m, 2H); 5.10 (s, 2H); 5.00 (t, 1H, $J = 5$); 4.17 (d, 2H, $J = 6$); 4.16−4.11 (m, 1H); 3.21−3.15 (m, 2H); 2.05−1.8 (m, 2H); 1.54−1.42 (m, 4H). ^{13}C NMR, δ: 168.2; 157.3; 136.7; 130.0; 128.4; 128.1; 128.0; 119.8; 67.0; 60.4; 43.1; 39.4; 29.6; 29.2; 21.2. Exact mass (EI): 381.1346; calcd 381.1358.

2-Butyl-4*S*-(benzyl-4-butylcarbamate)-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 5k. ^{1}H NMR ($CDCl_3$), δ: 7.37−7.30 (m, 5H); 6.23 (d, 1H, $J = 5$); 5.09 (s, 2H); 5.04 (br s, 1H); 4.11 (m, 1H); 3.57 (t, 2H, $J = 7$); 3.22−3.15 (m, 2H); 2.10−1.76 (m, 2H); 1.75−1.66 (q, 2H); 1.54−1.45 (m, 4H); 1.45−1.30 (m, 2H); 0.93 (t, 3H, $J = 7$). ^{13}C NMR, δ: 168.7; 157.4; 136.3; 128.6; 128.3; 128.2; 67.1; 60.4; 41.0; 29.9; 19.9; 13.5. Exact mass (EI): 397.1664; calcd 397.1671.

2-(4-Methoxyphenetyl)-4*S*-(benzyl-4-butylcarbamate)-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 5l. ^{1}H NMR ($CDCl_3$), δ: 7.38−7.31 (m, 5H); 7.17 and 6.84 (2d, 4H, $J = 9$); 6.23 (d, 1H, $J = 5$); 5.13 (d, 2H, $J = 4$); 4.92 (m, 1H); 4.12 (m, 1H); 3.84 3.70 (m, 2H); 3.78 (s, 3H); 3.24−3.16 (m, 2H); 2.99 (t, 2H, $J = 8$); 2.06−1.79 (m, 2H); 1.55−1.45 (m, 2H); 1.40−1.30 (m, 2H). ^{13}C NMR, δ: 168.3; 158.4; 157.2; 136.2; 129.9; 129.2; 128.5; 128.1; 128.0; 113.9; 66.9; 60.3; 55.1; 42.1; 39.6; 33.1; 29.8; 29.2; 21.2. Exact mass (EI): 475.1771; calcd 475.1777.

2-Chloroethyl-4*S*-(2-benzyloxycarbonylethyl)-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 5m. ^{1}H NMR ($CDCl_3$), δ: 7.36 (s, 5H); 5.13 (s, 2H); 4.26 (t, 1H, $J = 6$); 3.94 (t, 2H, $J = 7$); 3.75 (t, 2H, $J = 7$); 2.65−2.54 (m, 2H); 2.33−2.24 (m, 2H). MS (ESI, negative ion), *m*/*z*: 359 $(M - 1)^-$; calcd 360.05.

2-Allyl-4*S*-(2-benzyloxycarbonylethyl)-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 5n. ^{1}H NMR ($CDCl_3$), δ: 7.35 (s, 5H); 6.03 (d, 1H, $J = 6$); 5.95−5.78 (m, 1H); 5.40−5.26 (m, 2H); 5.14 (s, 2H); 4.30−4.26 (m, 1H); 4.18 (d, 2H, $J = 6$); 2.61 (t, 2H, $J = 7$); 2.38−2.08 (m, 2H). ^{13}C NMR, δ: 173.2; 167.8; 135.3; 128.7; 128.6; 128.4; 130.0; 120.2; 67.1; 59.9; 43.3; 30.1; 26.0. Exact mass (EI): 338.0930; calcd 338.0936.

2-(4-Methoxyphenetyl)-4*S*-(2-benzyloxycarbonylethyl)-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 5o. ^{1}H NMR ($CDCl_3$), δ: 7.37 (s, 5H); 7.15 and 6.86 (2d, 4H, $J = 9$); 6.01 (d, 1H, $J = 6$); 5.15 (s, 2H); 4.25−4.20 (m, 1H); 3.89−3.71 (d, 2H, $J = 6$); 3.79 (s, 3H); 2.97 (t, 2H, $J = 8$); 2.55−2.41 (m, 2H); 2.35−2.01 (m, 2H). ^{13}C NMR, δ: 173.5; 167.4; 158.4; 135.1; 129.8; 129.0; 128.6; 128.5; 128.4; 113.9; 67.1; 59.9; 55.1; 42.2; 33.1; 29.8; 25.4. Exact mass (EI): 432.1348; calcd 432.1355.

2-Butyl-4*S*-(2-benzyloxycarbonylethyl)-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 5p. ^{1}H NMR ($CDCl_3$), δ: 7.37 (s, 5H); 6.08 (d, 1H, $J = 6$); 5.13 (s, 2H); 4.27−4.23 (m, 1H); 3.58 (t, 2H, $J = 8$); 2.60 (t, 2H, $J = 7$); 2.35−2.09 (m, 2H); 1.77−1.65 (q, 2H); 1.41−1.30 (m, 2H). Exact mass (EI): 354.1244; calcd 354.1249.

2-Allyl-4*S*-(benzyloxy)methyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 5q. ^{1}H NMR ($CDCl_3$), δ: 7.32−7.19 (m, 5H); 5.9−5.75 (m, 1H); 5.34−5.20 (m, 2H); 5.16 (br s, 4.51); 4.56−4.46 (m, 2H); 4.15 (m, 3H); 4.05 (dd, 1H, $J = 3$ and $J = 7$); 4.15 (dd, 1H, $J = 3$ and $J = 7$). Exact mass (EI): 296.0836; calcd 296.0831.

Preparation of N^5-Substituted Sulfahydantoins 8. In each Quest tube, BOC deprotection of the initial resin (0.5 g, 0.3 mmol) was accomplished with 25% TFA in CH_2Cl_2 (30 min), followed by washing with DMF (3 × 8 mL), MeOH (3 × 8 mL), and CH_2Cl_2 (4 × 8 mL). For reductive alkylation, TMOF (8 mL), an aldehyde (3.3 mmol), and acetic acid (10 μL, 0.17 mmol) were added to the resins and the resulting mixtures were shaken for 1 h. Resins were then filtered and washed with CH_2Cl_2 (2 × 8 mL), and the reductive alkylation process was repeated a second time. Resins were then filtered and washed with CH_2Cl_2 (2 × 8 mL). $NaBH_3CN$ (7.5 mL of 0.2 M solution in TMOF, 1.5 mmol) and acetic acid (10 μL, 0.17 mmol) were added, and mixtures were agitated for 10 min. Resins were filtered and washed with DMF (3 × 8 mL), MeOH (3 × 8 mL), DMF (3 × 8 mL), and DCM (3 × 8 mL). *N*-Sulfamoylation was then achieved following conditions described above. In this case, the cyclization was performed by treating the resin with a 50% TFA solution in CH_2Cl_2. After 2 h of agitation, resins were filtered and rinsed with CH_2Cl_2 (2 × 8 mL) and the combined organic phase was evaporated to afford N^5-substituted sulfahydantoins **8**.

Salient Spectroscopic Data for Derivatives of 8. 5-(4-Cyanobenzyl)-4*S*-benzyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 8a. ^{1}H NMR ($CDCl_3$), δ: 7.52 and 7.28 (2d, 4H, $J = 7$); 7.20 (m, 5H); 6.10 (br s, 1H); 4.20 (d, 2H, $J = 6$); 4.09 (dd, 1H, $J = 4$ and $J = 10$); 3.27 (dd, 1H, $J = 4$ and $J = 15$); 3.11 (dd, 1H, $J = 10$ and $J = 15$). ^{13}C NMR, δ: 168.3; 139.1; 135.2; 132.5; 129.4; 129.3; 129.0; 127.6; 118.3; 112.3; 67.2; 51.4; 37.8. Exact mass (EI): 341.0834; calcd 341.0827.

5-(4-Methoxybenzyl)-4*S*-benzyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 8b. ^{1}H NMR ($CDCl_3$), δ: 7.37−7.15 (m, 5H); 7.02 and 6.79 (2d, 4H, $J = 9$); 5.95 (br s, 1H); 4.36 and 3.93 (2d, 2H, $J = 14$); 4.08 (dd, 1H, $J = 5$ and $J = 8$); 3.12−3.08 (m, 2H). Exact mass (EI): 346.0980; calcd 346.0987.

5-*p*-Nitrobenzyl-4*S*-benzyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 8c. ^{1}H NMR ($CDCl_3$), δ: 8.06 and 7.18 (2d, 4H, $J = 8$); 7.26−7.13 (m, 5H); 6.70 (br s, 1H); 4.30 and 4.16 (2d, 2H, $J = 15$); 4.10 (d, 1H, $J = 4$); 3.27 (dd, 1H, $J = 4$ and $J = 14$); 3.11 (dd, 1H, $J = 10$ and $J = 14$). ^{13}C NMR, δ: 168.4; 147.7; 140.9; 135.1; 129.3; 129.3; 129.0; 127.5; 123.7; 67.4; 51.2; 37.7. Exact mass (EI): 361.0739; calcd 361.0732.

5-(4-Methylbenzyl)-4*S*-benzyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 8d. ^{1}H NMR ($CDCl_3$), δ: 7.30−7.14 (m, 5H); 7.09 and 7.01 (2d, 4H, $J = 8$); 4.38 and 3.96 (2d, 2H, $J = 15$); 4.09 (dd, 1H, $J = 5$ and $J = 7$); 3.10−3.07 (m, 2H); 2.33 (s, 3H). ^{13}C NMR, δ: 168.5; 138.6; 135.2; 130.0; 129.7; 129.6; 129.2; 128.7; 127.4; 65.4; 50.6; 37.3; 21.2. Exact mass (EI): 330.10; calcd 330.10.

Preparation of N^2,N^5-Disubstituted Sulfahydantoins 10. After reductive amination and *N*-sulfamoylation described above, resins were washed with THF (3 × 8 mL). To the resins swollen in THF (7 mL), PPh_3 (0.9 mmol, 0.9 mL of 1.0 M solution in THF), an alcohol (0.9 mmol), and DIAD (0.18 mL, 0.9 mmol) were added under N_2. Mixtures were shaken for 1 h, then resins were filtered and washed with DMF (3 × 8 mL), MeOH (3 × 8 mL), and anhydrous CH_2Cl_2 (3 × 8 mL). BOC deprotection and cyclization were then performed by a 2 h treatment with a solution of 50% TFA in CH_2Cl_2. Resins were filtered and rinsed with CH_2Cl_2 (2 × 8 mL). The combined organic phases were evaporated to yield N^2,N^5-disubstituted sulfahydantoins **10**.

Salient Spectroscopic Data for Derivatives of 10. 2-Allyl-5-(4-methylbenzyl)-4*S*-benzyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 10a. ^{1}H NMR ($CDCl_3$), δ: 7.30−7.00 (m, 9H); 5.85−5.70 (m, 1H); 5.30−5.20 (m, 2H); 4.36 and 4.02 (2d, 2H, $J = 14$); 4.17−4.14 (m, 2H); 4.09−4.07 (m, 1H); 4.20 (m, 2H); 3.10−3.02 (m, 2H); 2.33 (s, 3H). ^{13}C NMR, δ: 166.0; 138.6; 135.1; 129.9; 129.9; 129.6; 129.3; 128.6; 127.4; 119.8; 64.5; 51.0; 43.0; 37.3; 21.1. Exact mass (EI): 370.1342; calcd 370.1351.

2-Butyl-5-(4-methylbenzyl)-4*S*-benzyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 10b. ^{1}H NMR ($CDCl_3$), δ: 7.30−7.00 (m, 9H); 4.36 and 4.03 (2d, 2H, $J = 14$); 4.07−4.03 (m, 1H); 3.55 (t, 2H, $J = 7$); 3.05−3.02 (m, 2H); 2.33 (s, 3H); 1.68−1.59 (m, 2H); 1.35−1.20 (m, 2H); 0.91 (t, 3H, $J = 7$). ^{13}C NMR, δ: 166.2; 138.6; 135.2; 130.0; 129.8; 129.6; 129.3; 128.6; 127.3; 64.5; 50.9; 41.0; 37.2; 29.8; 21.1; 19.8; 13.5. Exact mass (EI): 386.1657; calcd 386.1664.

2-Phenylpropyl-5-(4-methylbenzyl)-4*S*-benzyl-1,2,5-thiadiazolidin-3-one 1,1-Dioxide, 10c. ^{1}H NMR ($CDCl_3$), δ: 7.32−7.00 (m, 9H); 4.38 and 4.03 (2d, 2H, $J = 14$); 4.09−4.06 (m, 1H); 3.60 (t, 2H, $J = 7$); 3.10−3.03 (m, 2H); 2.58 (t, 2H, $J = 7$); 2.33 (s, 3H); 2.03−1.94 (q, 2H). ^{13}C NMR, δ: 166.3; 140.6; 138.6; 135.1; 130.0; 129.8; 129.6; 129.3; 128.6; 128.5; 128.4; 127.4; 126.1; 64.5; 50.9; 40.8; 37.2; 32.8; 29.3; 21.1. Exact mass (EI): 448.1831; calcd 448.1820.

Procedure for Enantiomeric Purity Determination. The level of racemization of the overall process was verified by ^{1}H NMR of diastereoisomeric derivatives of sulfahydantoins using (*R*)-(+)-methylbenzyl isocyanate. A typical procedure is as follows. Under N_2, a solution of sulfahydantoin (0.16 mmol) in dichloromethane was added to 1 equiv of (*R*)-(+)-methylbenzyl isocyanate in dichloromethane in the presence of 2 equiv of NEt_3 for 2 h at room temperature. Evaporation followed by coevaporation with Et_2O led to crude diastereomeric mixtures ready to be studied by NMR in $CDCl_3$.

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Supporting Information Available. ^{1}H NMR spectra of diastereoisomers. This material is available free of charge via the Internet at http://pubs.acs.org.

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