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Solution-phase parallel synthesis of highly diverse spiroisoxazolinohydantoins

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Abstract

Practical and efficient solution-phase parallel synthesis of spiroisoxazolinohydantoins under mild conditions has been developed. This spiroisoxazolinohydantoin skeleton possesses three diversity points. The key intermediate, *exo*-methylenehydantoin bearing two positions of diversification, is prepared via a one-pot synthetic route from N-substituted methyl ester serine. Employing various alkyl halides, isocyanates, and oximes, this chemistry is applied in the generation of an 18-member demonstration library with high yield, high purity and excellent regioselectivity.

Keywords: Spiro compounds; Solution-phase combinatorial chemistry; Isoxazoline; Hydantoin

Small molecule combinatorial chemistry has dramatically accelerated the progress of developing biologically interesting molecules in chemical biology and drug discovery.[1] To efficiently prepare small molecule libraries, solid- or solution-phase organic synthesis[1] and various techniques,[2] such as fluorous tag approach[2a] and solid-phase extraction,[2b] have been extensively developed.

Compared to solid-phase organic synthesis, solution-phase organic synthesis is more suitable for the preparation of relatively small and focused libraries since it enjoys several advantages; for example, (1) easy analysis or monitor of the reaction progress; (2) favorable reaction kinetics in homogeneous conditions; and (3) rapid development of chemical synthetic routes. However, the time-consuming purification is its disadvantage but, fortunately, several strategies, such as the 'smart design' based on chemical efficiency[3] and automatic purification,[4] have been provided to overcome this limitation.

From the chemical structure point of view, various natural products or synthetic molecules containing the rigid conformations of spirocyclic skeletons show a wide range of biological properties.[1a,5] For example, spirohydantoins have been reported as glycogen phosphorylase inhibitors, herbicides, and anti-inflammatory agents as shown in Figure 1.[6] Additionally, spiroisoxazoline natural products involving diverse antimicrobial, cytotoxic, and anti-inflammatory activities have also been identified as a new class of novel alkaloids from marine sponge (Fig. 1).[7] Due to their broad-spectrum biological activities, the spirocyclic cores have been considered as privileged scaffolds for drug design.[1a] Not surprisingly, many spirocarbocyclic hydantoins or spirocarbocyclic isoxazolines synthesis have been extensively studied by Park and Kurth,[8] McCurdy and co-workers,[9] and others.[10] In contrast, to the best of our knowledge directly fusing both hydantoin and isoxazoline to efficiently generate a spirocyclic skeleton in a novel hybrid template has not been completely explored.[11] As part of our research interests is to design and synthesize small molecule libraries via solid- or solution-phase combinatorial approach. Herein, we report an efficient solution-phase parallel synthetic method under mild reaction conditions for combining these two interesting structural features within a single framework to form spiroisoxazolinohydantoins **1**

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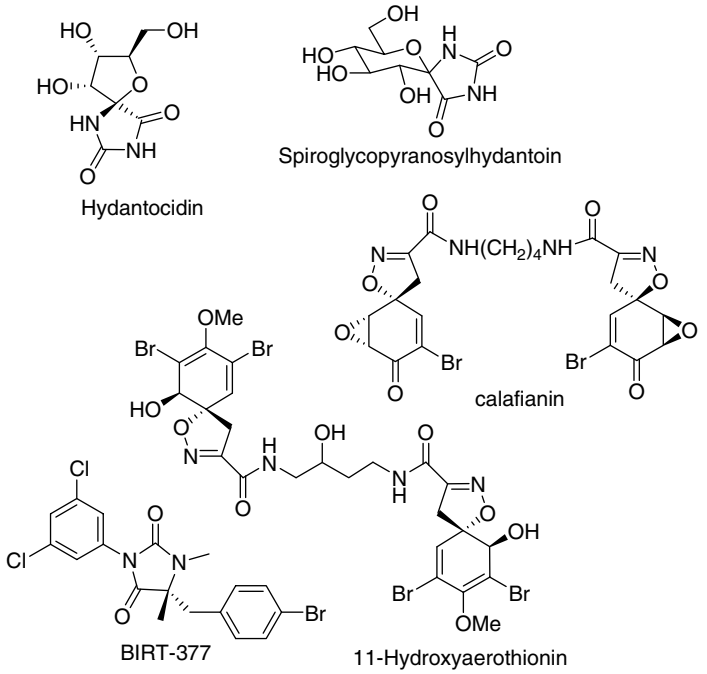


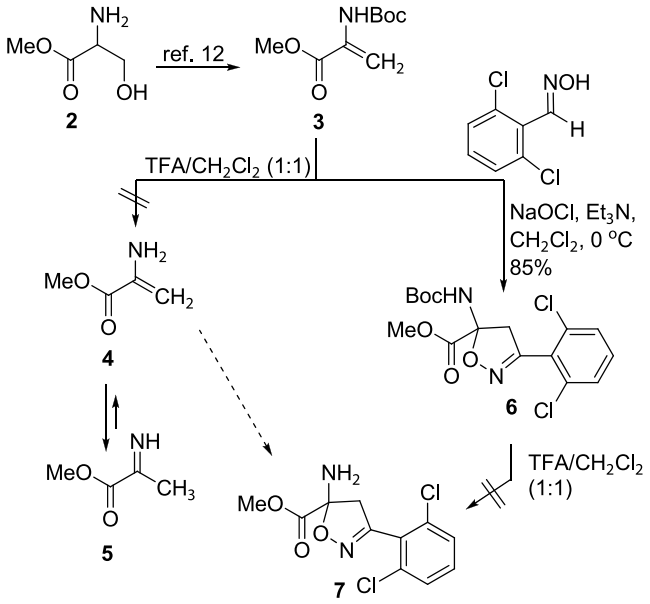
Fig. 1. Examples of bioactive molecules containing spirohydantoin or spiroisoxazoline scaffolds.

with three points of substitution diversity (R^1, R^2, and R^3 in **1**, see Fig. 2).

Our synthetic effort started with commercially available DL-serine methyl ester (**2**). *N*-Boc protected dehydroalanine methyl ester **3** was obtained through a multi-step procedure via *N*-Boc protection, O-mesylation, and β-elimination (Scheme 1).[12]

Initially attempts to deprotect the Boc protected amine **3** followed by 1,3-dipolar cycloaddition with 2,6-dichlorobenzaldehyde oxime in the presence of NaOCl (the Huisgen method for in situ nitrile oxide generation)[13] were not successful. Presumably, vinyl amine **4** would tautomerize to imine **5** which was labile in aqueous solution during 1,3-dipolar cycloaddition.[14] To circumvent this problem, our synthetic route was modified to proceed 1,3-dipolar cycloaddition first to smoothly generate **6** bearing an isoxazoline ring in 85% yield from **2**. Based on preliminary literature studies,[15,16] we were not surprised to find that **3**→**6** proceeded with complete regioselectivity (none of the regioisomer could be detected). However, upon treatment with TFA/DCM in various ratios to undergo *N*-Boc deprotection, the reaction was messy and not successful. Even under neutral conditions, ceric ammonium nitrate, resul continued to decomposition.[17]

These disappointing observations led us to switch reactions to accomplish hydantoin formation followed by 1,3-dipolar cycloaddition (Fig. 3). Based on our literature studies, only few examples regarding 5-methylenehydantoins have been disclosed.[18] Surprisingly, we were not aware



Scheme 1. An attempted synthetic route for **7**.

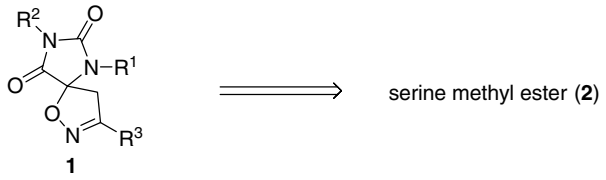


Fig. 2. Spiroisoxazolinohydantoins from serine methyl ester.

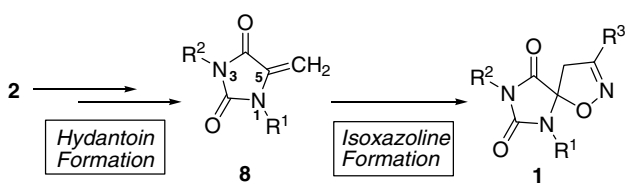
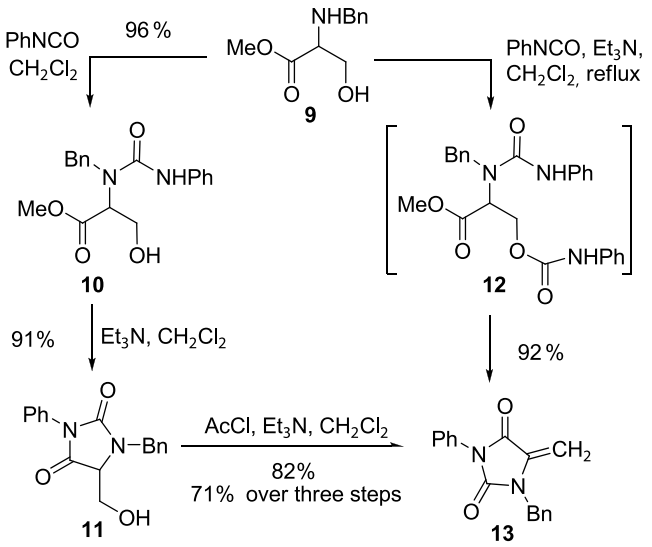
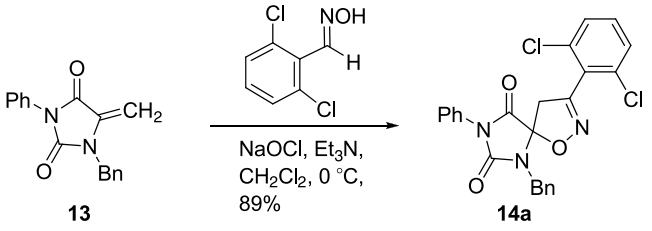


Fig. 3. General synthetic route.



Scheme 2. Preparation of *exo*-methylenehydantoin **13**.



Scheme 3. Preparation of spiroisoxazolinohydantoin **14a**.

of any practical method to prepare 5-methylenehydantoins **8** with two points of diversification (R^1, R^2 = alkyl or aromatic group; $R^1 \neq R^2$; see in Fig. 3). Thus, how to develop an efficient synthetic route for the key intermediate **8** was our first task.

Treatment of *N*-benzyl methyl ester serine **9**,[19] obtained from N-alkylation of **2** with benzyl bromide, with phenyl isocyanate (1 equiv) gave urea **10**, followed by cyclization under basic conditions (Et_3N/CH_2Cl_2) to deliver serine hydantoin **11**. Subsequent base-mediated O-acetylation of **11** with concomitant elimination of the O-acylated group furnished *N*1-benzyl-*N*3-phenyl-5-methylenehydantoin **13** as shown in Scheme 2. In contrast, treatment of **9** with phenyl isocyanate (2.2 equiv) and Et_3N at room temperature for 2 h followed by warming the reaction mixture to 50 °C for 4 h directly gave **13** in good yield (92%) after solid-phase extraction.[20] We were pleased to point out this one-pot synthetic route was the most convenient way to prepare 5-methylenehydantoins **8** bearing two position of diversification ($R^1 \neq R^2$) (see Scheme 3).

With the *exo*-methylenehydantoin **13** in hand, the 1,3-dipolar cycloaddition reaction with the nitrile oxide was carried out (generated in situ from 2,6-dichlorobenzaldehyde oxime).[13,15,16] Fortunately, after simple extraction without further purification, the desired spiroisoxazolinohydantoin **14a** (R^1 = benzyl; R^2 = phenyl; R^3 = 2,6-dichlorobenzyl) was delivered in high yield (89%) and high purity (92%). As expected, this reaction performed the excellent regioselectivity to give essentially a single regioisomer **14a** from ^{1}H NMR analysis of the crude reaction mixture.[21]

To demonstrate this efficient and straightforward procedure to prepare spiroisoxazolinohydantoins, we built a small library ($2 \times 3 \times 3$)[22] for 18 distinct compounds as shown in Table 1. Following this general protocol we developed, all of desired molecules were prepared in high yields and high purities.

In summary, we developed a practical and efficient solution-phase parallel synthetic route for spiroisoxazolinohydantoins with three diversity points. The key intermediate, *exo*-methylenehydantoin, is generated via a one-pot synthetic route from N-substituted methyl ester serine. All the chemical transformations are highly effective under mild reaction conditions. Employing various alkyl halides, isocyanates, and oximes, this

Table 1
A small library of spiroisoxazolinohydantoins with three diversity points

Product	R^1 (alkyl halide)	R^2 (isocyanate)	R^3 (oxime)	Yield (purity)[a] (%)
14a	Benzyl	Phenyl	2,6-Dichlorobenzyl	89 (92)
14b	Benzyl	Phenyl	4-Bromobenzyl	87 (83)
14c	Benzyl	Phenyl	2,5-Dimethoxybenzyl	82 (80)
14d	Benzyl	Cyclohexanyl	2,6-Dichlorobenzyl	83 (92)
14e	Benzyl	Cyclohexanyl	4-Bromobenzyl	82 (>97)
14f	Benzyl	Cyclohexanyl	2,5-Dimethoxybenzyl	85 (81)
14g	Benzyl	Propanyl	2,6-Dichlorobenzyl	85 (89)
14h	Benzyl	Propanyl	4-Bromobenzyl	82 (>97)
14i	Benzyl	Propanyl	2,5-Dimethoxybenzyl	83 (71)
14j	4-Bromobenzyl	Phenyl	2,6-Dichlorobenzyl	86 (>97)
14k	4-Bromobenzyl	Phenyl	4-Bromobenzyl	87 (>97)
14l	4-Bromobenzyl	Phenyl	2,5-Dimethoxybenzyl	84 (>97)
14m	4-Bromobenzyl	Cyclohexanyl	2,6-Dichlorobenzyl	92 (92)
14n	4-Bromobenzyl	Cyclohexanyl	4-Bromobenzyl	91 (>97)
14o	4-Bromobenzyl	Cyclohexanyl	2,5-Dimethoxybenzyl	90 (93)
14p	4-Bromobenzyl	Propanyl	2,6-Dichlorobenzyl	89 (>97)
14q	4-Bromobenzyl	Propanyl	4-Bromobenzyl	84 (73)
14r	4-Bromobenzyl	Propanyl	2,5-Dimethoxybenzyl	88 (>97)

[a] HPLC purity of crude product ($\lambda = 220$ nm).

chemistry is applied in the generation of an 18-member library with high yield, high purity, and excellent regioselectivity.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.12.008.

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20. Typical procedure for the transformation (**9**→**13**): To a solution of **9** (0.26 g, 0.94 mmol) in CH_2Cl_2 (5 mL) under a nitrogen atmosphere at 0 °C was added phenyl isocyanate (0.33 g, 2.81 mmol, 3 equiv) and triethylamine (0.47 g, 4.68 mmol). The mixture was stirred for 30 min at room temperature, then warmed to 50 °C and stirred overnight. The product was diluted with CH_2Cl_2 and washed with water several times. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was washed with CH_2Cl_2 by normal phase (silica gel) solid-phase extraction to give **13** (0.24 g, 0.86 mmol, 92%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$, ambient temperature) δ 4.79 (d, 1H, $J = 2.4$ Hz), 4.86 (s, 2H), 5.46 (d, 1H, $J = 2.4$ Hz), 7.24–7.52 (m, 10H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.75, 155.36, 136.06, 131.81, 128.56, 128.40, 128.13, 128.07, 127.79, 126.63, 105.08, 47.01; HRMS calcd for $C_{17}H_{14}N_2O_2$ $[M+H]^+$ 279.1134, found 279.1144.
21. Typical procedure for the transformation (**13**→**14a**): **13** (0.24 g, 0.86 mmol) and 2,6-dichlorobenzaldehyde oxime (0.16 g, 0.86 mmol, 1 equiv) were dissolved in CH_2Cl_2 (4 mL) and the solution was cooled to 0 °C. Aqueous NaOCl (5%, 2 equiv, 2.5 g, 1.72 mmol) was added dropwise over 30 min, and the reaction mixture was stirred vigorously for 8 h (0 °C→room temperature). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated to give **14a** (0.36 g, 0.76 mmol, 89%) as a white solid and characterized without further purification. **14a**: ^{1}H NMR (600 MHz, $CDCl_3$, ambient temperature) δ 3.30 (d, 1H, $J = 18$ Hz), 3.77 (d, 1H, $J = 18$ Hz), 4.67 (d, 1H, $J = 18$ Hz), 4.87 (d, 1H, $J = 18$ Hz), 7.15–7.45 (m, 13H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.83, 31.04, 41.34, 43.87, 95.38, 125.83, 126.83, 127.60, 127.81, 127.95, 128.08, 128.23, 128.48, 128.54, 128.79, 128,96, 129.25, 131.24, 131.94, 135.24, 136.36, 153.95, 154.63, 168.23; HRMS calcd for $C_{24}H_{17}Cl_2N_3O_3[M + H]^+$ 466.0725, found 466.0757.
22. Two alkyl halides (benzyl bromide and 4-bromobenzyl bromide), three isocyanates (phenyl isocyanate, propanyl isocyanate, and cyclohexanyl isocycanate), and three oximes (2,6-dichlorobenzaldehyde oxime, 4-bromobenzaldehyde oxime, and 2,5-dimethoxybenzaldehyde oxime) were utilized for diversification of R^1, R^2 and R^3, respectively.