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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.
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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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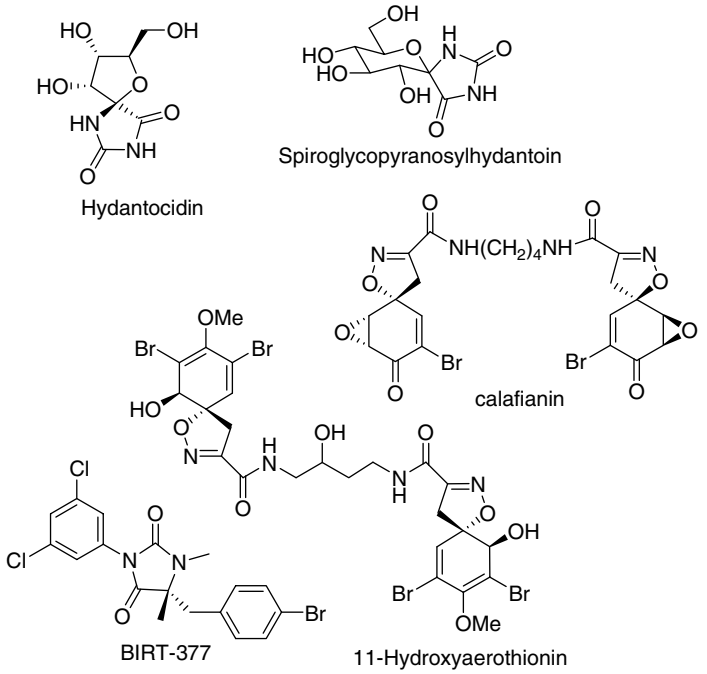


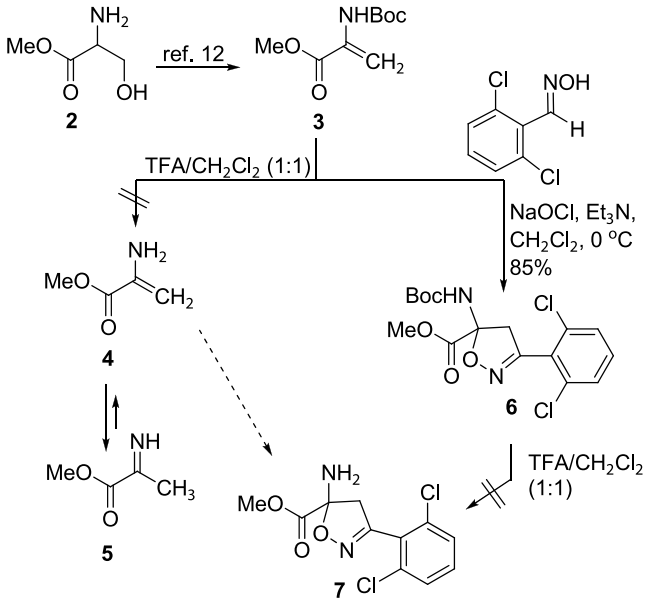
Fig. 1. Examples of bioactive molecules containing spirohydantoin or spiroisoxazoline scaffolds.

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**.

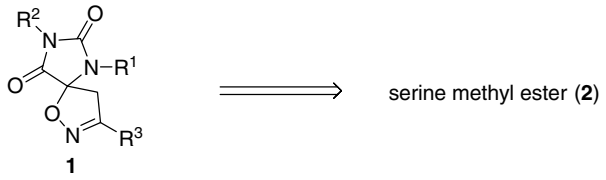


Fig. 2. Spiroisoxazolinohydantoins from serine methyl ester.

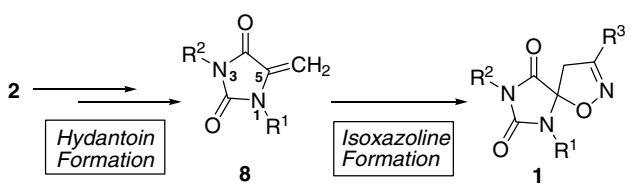


Fig. 3. General synthetic route.

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