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Solid-phase synthesis of α-substituted proline hydantoins and analogs

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Abstract—The manual solid-phase preparation of racemic α-substituted bicyclic proline hydantoins and analogs, which can potentially contain up to four sites of structural diversity (ring size and substitution on the ring or at the ring fusion), is described. Key steps involved alkylation of aldimines of resin-bound amino acids with α,ω-dihaloalkanes and intramolecular displacement of the halide to generate α-substituted prolines and homologs. After formation of resin-bound ureas by reaction of these sterically-hindered secondary amines with isocyanates, base-catalyzed cyclization/cleavage yielded the desired hydantoin products.

1. Introduction

Hydantoin derivatives have attracted much interest in drug discovery because of their wide range of therapeutic properties.[1] This five-membered rigid heterocycle **1**, with four possible points of diversity, represents a significant molecular scaffold in combinatorial chemistry (Fig. 1).

From the early days[2] of combinatorial chemistry to recent years, numerous solid-phase syntheses (SPS) of hydantoins have been reported using natural and unnatural acyclic α-amino acids as starting building blocks.[3]

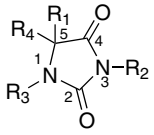

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Figure 1. Generic structure for hydantoins.

This solid-phase methodology has also been used, but in a much more limited fashion, to construct conformationally constrained hydantoin-containing polycyclic scaffolds (Fig. 2). For example, SPS of proline hydantoin **2**[4] and 3-substituted tetrahydroisoquinoline hydantoins **3**[5] were reported as representative structures in early publications describing novel methodologies. Thereafter, SPS of a diverse number of 1-substituted tetrahydroisoquinoline hydantoins **4**,[6] tetrahydro-β-carboline hydantoins **5**,[7] 2,5,6,7-tetrasubstituted-1*H*-pyrrolo[1,2-*c*]imidazoles **6**,[8] and hexahydro-2,3a,7-triazacyclopenta[*c*]pentalene-1,3-diones **7**[9] have been reported.

We have described methods for the preparation of resin-bound α-substituted prolines and homologs **13** (Scheme 1),[10] which are conformationally restricted cyclic amino acid derivatives. Recognizing that these α-substituted proline homologs could be key components of polycyclic scaffolds, and given the limited availability by solid-phase techniques of these basic structural types, we sought to prepare the more conformationally constrained and varied bicyclic scaffolds **8** (Fig. 3), by fusing the hydantoin ring at the N-1 and C-5 positions to a functionalized five-membered pyrrolidine ring and homologs (ring size = 5 to 7). Herein we describe the manual solid-phase preparation of racemic α-substituted proline hydantoins **8** and analogs, which can potentially contain up to four sites of structural diversity (N-3 and C-5 positions, pyrrolidine ring size and ring substitution).[11]

Keywords: Alkylation; Amino acid; Combinatorial chemistry; Cyclative cleavage; α,ω-Dihaloalkanes; Hydantoin; Proline; Solid-phase.
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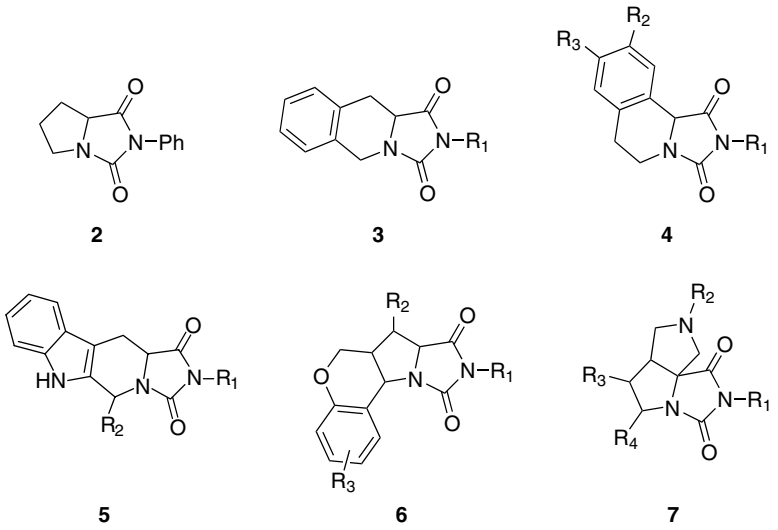
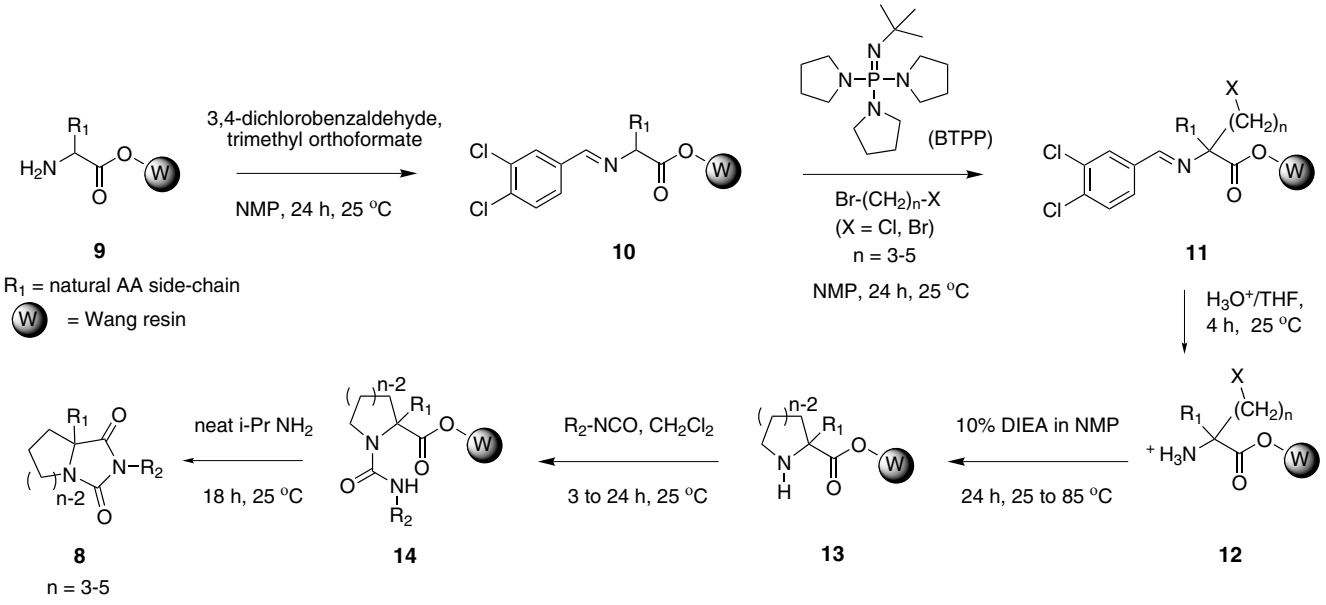


Figure 2. Hydantoin-containing polycyclic scaffolds previously prepared using solid-phase methods.



Scheme 1. Synthesis of resin-bound α-substituted proline and homologs **13**, followed by formation of α-substituted proline hydantoins **8** by urea formation and subsequent cyclative cleavage.

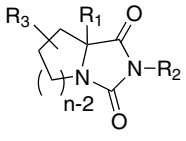


Figure 3. Generic structure for α-substituted proline hydantoins.

2. Results and discussion

The overall sequence to hydantoins **8** is shown in Scheme 1. Resin-bound α-substituted proline and its ring homologs **13** bearing natural amino acid side chains were prepared by the following synthetic sequence:[10] (i) activation of the α-position of resin-bound amino acids by conversion to the aldimine-derived Schiff base **10**; (ii) alkylation with α,ω-dihaloalkanes of different chain lengths ($n = 3-5$) to provide racemic intermediates **11**; (iii) mild acid-catalyzed hydrolysis of the imine to give **12**; and (iv) neutralization of the amine salt and subsequent intramolecular displacement of the halide by the α-amino group to form **13**. As previously described,[10] resin-bound five- and six-membered α-substituted proline ring homologs were prepared using α-bromo-ω-chloroalkanes for the alkylation and room temperature cyclization. The seven-membered ring product required use of the intermediate ω-bromo derivative from 1,5-dibromopentane and higher temperature (85 °C) during cyclization.