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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]

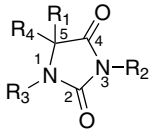

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Figure 1. Generic structure for hydantoins.

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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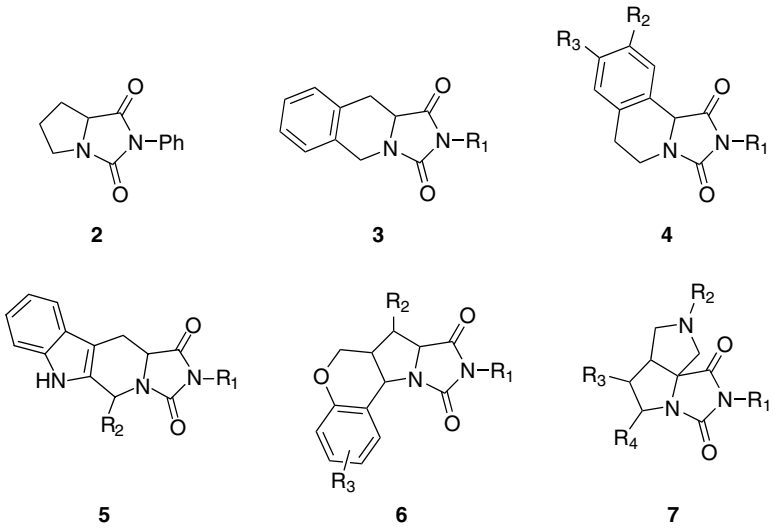
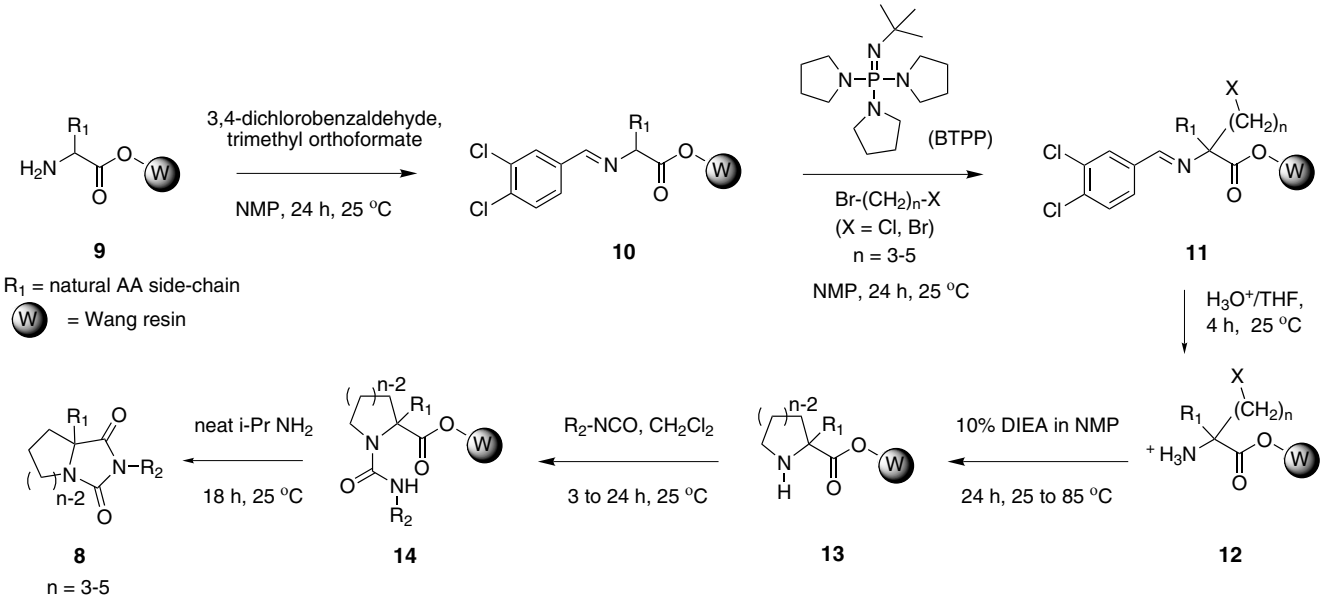


Figure 2. Hydantoin-containing polycyclic scaffolds previously prepared using solid-phase methods.



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.

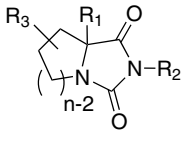


Figure 3. Generic structure for α-substituted proline hydantoins.

2. Results and discussion

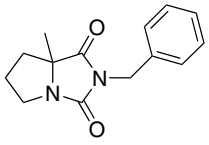
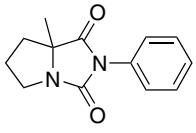
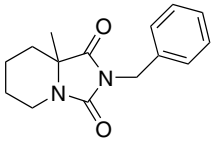
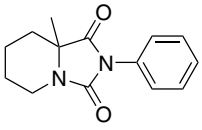
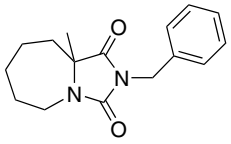
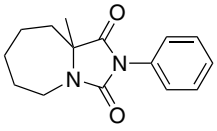
The overall sequence to hydantoins **8** is shown in Scheme 1. Resin-bound α-substituted proline and its ring homologs **13** bearing natural amino acid side chains were prepared by the following synthetic sequence:[10] (i) activation of the α-position of resin-bound amino acids by conversion to the 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.

The final steps of the synthesis involved acylation of the cyclic secondary amine **13** with a substituted isocyanate to generate a urea precursor **14**, followed by a mild base-mediated cyclative cleavage[5,6,8,9,12] from the resin with simultaneous hydantoin formation (Scheme 1). Formation of urea from the sterically demanding amine was accomplished using the representative phenyl or benzyl isocyanates (3 or 24 h, respectively). In the first case, longer reaction times led to lower purities of the final products.[13] In the second case, higher chemical yields with similar purities were achieved by extending the acylation time with benzyl isocyanate. Final treatment of the resin-bound ureas with neat isopropylamine[12c] gave the desired protected α-substituted proline hydantoins and analogs **8**.

Representative structures prepared by this method, starting from commercially available Fmoc-AA-Wang resins, are shown in Tables 1 and 2. The HPLC purity (UV detection at 220 nm) of the crude products **8a**–**n** ranged from 84% to 96%, with isolated, purified yields from 36% to 74%. Yields and purities appear to be relatively insensitive to the amino acid side-chain functionality present and the substituted isocyanate used. The best chemical yields were generally obtained with the bicyclic [5,5] system.

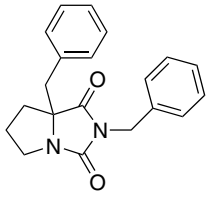
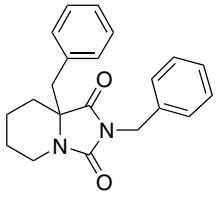
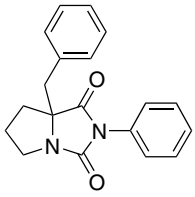
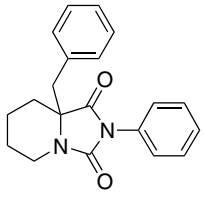
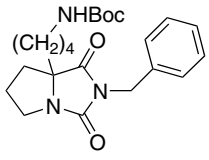
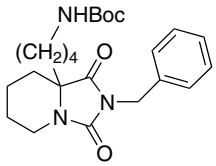
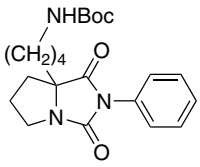
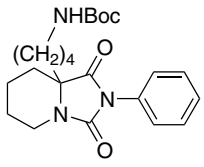
In summary, bicyclic hydantoin-containing scaffolds with three points of diversity have been prepared starting from resin-bound amino acids. Even greater structural diversity could be obtained by using our published methods[10,14] for the preparation of resin-bound unnatural amino acids (variation at the C-5 position) and/or by the presence of substituents on the pyrrolidine ring and homologs.

Table 1. α-Substituted proline hydantoins and analogs prepared from Fmoc-Ala-Wang-resin

[5,5]	 **8a** (91%,74%)	 **8d** (92%,72%)
[6,5]	 **8b** (91%,62%)	 **8e** (91%,58%)
[7,5]	 **8c** (85%,36%)	 **8f** (92%,62%)

Compound number (crude HPLC purity, isolated yield).

Table 2. Side-chain protected α-substituted proline hydantoins and analogs prepared from Fmoc-Phe-Wang-resin and Fmoc-Lys(Boc)-Wang resin

	[5,5]	[6,5]
Phe	 **8g** (91%,68%)	 **8h** (87%,68%)
	 **8i** (86%,74%)	 **8j** (84%,49%)
Lys	 **8k** (94%,60%)	 **8l** (94%,53%)
	 **8m** (92%,71%)	 **8n** (96%,57%)

Compound number (crude HPLC purity, isolated yield).

3. Experimental

3.1. General methods

Solid-phase reactions were conducted as described previously.[10] Analytical HPLC was performed using a Nova-Pak® Waters C_{18} reversed-phase column (3.9 × 150 mm) on a Varian 9010 instrument, and linear gradients of 0.1% TFA in CH_3CN and 0.1% aqueous TFA were run at 1.0 mL/min flow rate from 0:1 to 3:2 over 25 min. UV detection was at 220 nm. The isolated yields of final compounds, after silica gel filtration, are based on the mass of product and are relative to the initial loading of the starting Wang resins.

3.2. Preparation of the 3,4-dichlorobenzaldehyde imine of Ala-Wang-resin (10)

Fmoc-Ala-Wang-resin (0.1 g, 0.74 mmol/g) was washed with CH_2Cl_2 and DMF (2 × 1 min each), and then treated with piperidine–DMF (1:4, 1 × 1 min, 1 × 20 min), followed by washings with DMF (6 × 0.5 min). 3,4-Dichlorobenzaldehyde (194 mg, 15 equiv) was dissolved

in NMP-trimethyl orthoformate (1:2, 1.5 mL) and added to the resin, and the reaction was allowed to proceed for 24 h at 25 °C with rotation. The resultant resin-bound Schiff base product was washed with NMP and THF (4 × 0.5 min each).

3.3. Alkylation of resin 10 with an α,ω-dihaloalkane

Resin-bound Schiff base **10** (74 μmol) was washed with NMP (2 × 0.5 min). The α,ω-dihaloalkane (10 equiv) in NMP (1.2 mL) and BTPP (226 μL, 10 equiv) were added, and the suspension was rotated for 24 h at 25 °C. The resin was washed with NMP and CH_2Cl_2 (4 × 0.5 min each).

3.4. Hydrolysis of the imine

Resin-bound imine **11** (74 μmol) was washed with THF (6 × 0.5 min). THF–1 N aqueous HCl (2:1, 2.5 mL) was added, and the suspension was rotated for 4 h at 25 °C. The resin was filtered and washed with THF and CH_2Cl_2 (4 × 0.5 min each).

3.5. Intramolecular cyclization of the resin-bound alkylated products

The resin-bound amine **12** (74 μmol) was washed with NMP (4 × 0.5 min). Then, 10% DIEA in NMP (2 mL) was added to the resin, and the reaction mixture was rotated for 24 h at 25 °C. The resin was washed with NMP (4 × 0.5 min).

3.6. Urea formation by reacting resin-bound α-substituted proline and homologs with substituted isocyanates

The resin-bound secondary amine **13** (74 μmol) was washed with CH_2Cl_2 (4 × 0.5 min). Benzyl isocyanate (91 μL, 10 equiv) in CH_2Cl_2 (2 mL) was added, and the reaction mixture was rotated at 25 °C for 24 h. The resin-bound urea was washed with CH_2Cl_2 and NMP (4 × 0.5 min each).

3.7. Cyclative cleavage and purification

The resin-bound urea **14** was washed with CH_2Cl_2 (4 × 0.5 min each). Neat isopropylamine (2 mL) was added, and the suspension was rotated for 18 h at 25 °C. The filtrate was collected, combined with CH_2Cl_2 washes (4 × 1 mL) of the resin, and evaporated to dryness. The crude residue product was purified by filtration through a short column of silica gel with $CHCl_3$–THF(1:1, 50 mL total) to provide the desired hydantoin.

3.8. 2-Benzyl-7a-methyl-tetrahydro-pyrrolo[1,2-*c*]-imidazole-1,3-dione (8a)

Prepared as described above, using 1-bromo-3-chloropropane (73 μL, 10 equiv) in the alkylation step, to provide an amorphous white solid (13.3 mg, 74% isolated yield) following purification: initial HPLC purity 91%, t_R = 8.0 min. ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.62–1.88 (m, 2H), 1.90–2.18 (m, 2H), 3.12–3.26 (m, 1H), 3.58–3.72 (m, 1H), 4.54 (s, 2H), 7.15–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.8, 26.1, 33.5, 42.5, 44.6, 69.0, 127.8, 128.3, 128.7, 136.1, 159.8, 176.4.

3.9. 2-Benzyl-8a-methyl-tetrahydro-imidazo[1,5-*a*]-pyridine-1,3-dione (8b)

Prepared as described above, using 1-bromo-4-chlorobutane (85 μL, 10 equiv) in the alkylation step, to provide an amorphous white solid (11.9 mg, 62% isolated yield) following purification: initial HPLC purity 91%, t_R = 8.8 min. ^{1}H NMR ($CDCl_3$) δ 1.29–1.46 (m, 2H), 1.39 (s, 3H), 1.54-1.94 (m, 4H), 2.83 (dt, J_1 = 13.2 Hz, J_2 = 3.0 Hz, 1H), 4.08 (dd, J_1 = 13.8 Hz, J_2 = 5.1 Hz, 1H), 4.63 (s, 2H), 7.18–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.4, 19.4, 25.3, 32.4, 37.0, 42.2, 59.7, 127.7, 128.3, 128.6, 136.5, 154.1, 177.0.

3.10. 9a-Methyl-2-phenyl-hexahydro-imidazo[1,5-*a*]-azepine-1,3-dione (8f)

Prepared as described above, using 1,5-dibromopentane (101 μL, 10 equiv) in the alkylation step, 10% DIEA in NMP (2 mL) in the intramolecular cyclization [heating at 85 °C for 24 h with occasional agitation], and phenyl isocyanate (81 μL, 10 equiv) in CH_2Cl_2 (2 mL) for 3 h at 25 °C during the urea formation, to provide an amorphous white solid (11.8 mg, 62% isolated yield) following purification: initial HPLC purity 92%, t_R = 8.0 min. ^{1}H NMR ($CDCl_3$) δ 0.96–1.37 (m, 2H), 1.46 (s, 3H), 1.51–2.00 (m, 5H), 2.51–2.64 (m, 1H), 2.79–2.94 (m, 1H), 4.01–4.12 (m, 1H), 7.31–7.52 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.8, 23.9, 27.4, 29.7, 38.6, 40.5, 64.8, 126.0, 127.9, 128.9, 132.0, 154.8, 175.8.

3.11. 2,7a-Dibenzyl-tetrahydro-pyrrolo[1,2-*c*]imidazole-1,3-dione (8g)

Prepared as described above, starting with Fmoc-Phe-Wang-resin (0.1 g, 1.0 mmol/g) and using 1-bromo-3-chloropropane (99 μL, 10 equiv) in the alkylation step, to provide an amorphous white solid (21.7 mg, 68% isolated yield) following purification: initial HPLC purity 91%, t_R = 12.5 min. ^{1}H NMR ($CDCl_3$) δ 1.88–2.12 (m, 4H), 2.88 (d, J = 13.5 Hz, 1H), 3.15 (d, J = 13.5 Hz, 1H), 3.18–3.31 (m, 1H), 3.64–3.90 (m, 1H), 4.36 (d, J = 14.7 Hz, 1H), 4.49 (d, J = 14.7 Hz, 1H), 6.76–6.86 (m, 2H), 7.04–7.22 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 26.1, 32.8, 40.9, 42.2, 44.9, 73.4, 127.2, 127.3, 127.5, 128.3, 128.5, 130.2, 134.6, 135.5, 159.9, 175.3.

3.12. [4-(2-Benzyl-1,3-dioxo-tetrahydro-pyrrolo[1,2-*c*] imidazol-7a-yl)-butyl]-carbamic acid *tert*-butyl ester (8k)

Prepared as described above, starting with Fmoc-Lys-(Boc)-Wang-resin (0.1 g, 0.66 mmol/g) and using 1-bromo-3-chloropropane (65 μL, 10 equiv) in the alkylation step, to provide an amorphous white solid (15.8 mg, 60% isolated yield) following purification: initial HPLC purity 94%, t_R = 13.4 min. ^{1}H NMR ($CDCl_3$) δ 0.85–1.06 (m, 1H), 1.10–1.27 (m, 1H), 1.27–1.48 (m, 2H), 1.42 (s, 9H), 1.49–1.65 (m, 1H), 1.74–1.91 (m, 3H), 1.91–2.15 (m, 2H), 2.86–3.02 (m, 2H), 3.07–3.21 (m,

1H), 3.65–3.82 (m, 1H), 4.34 (br s, 1H), 4.58 (s, 2H), 7.20–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.1, 26.0, 28.4, 29.7, 33.0, 34.7, 40.2, 42.6, 44.8, 72.3, 79.1, 127.9, 128.4, 128.6, 136.1, 155.9, 160.2, 175.9.

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13. (a) When acylation with phenyl isocyanate was carried out for 24 h, we have evidence for the presence of 1-isopropyl-3-phenyl-urea in the crude product. This may have come from isopropylamine cleavage of an intermediate resin-bound carbamate. This, in turn, may have been produced when phenylisocyanate reacted with the hydroxymethyl-resin derived from premature hydantoin formation. (b) It has been noted that ureas derived from N-alkyl amino acids and aryl isocyanates cyclize more rapidly than those from alkyl isocyanates. See, Sim, M. M.; Ganesan, A. *J. Org. Chem.* **1997**, *62*, 3230–3235.
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