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Solid-phase synthesis of 3-aminohydantoin, dihydrouracil, thiohydantoin and dihydrothiouracil derivatives

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Abstract

An efficient and convenient route to 3-aminohydantoins and dihydrouracils using solid-phase chemistry has been developed. This methodology has the advantage of generality and diversity over solution-phase chemistry for the preparation of 3-aminohydantoins and dihydrouracils.

Hydantoin and aminohydantoin-containing heterocycles show a broad range of biological activity including anticonvulsant, antibacterial, antifungal, antiarrhythmic, antiherbicidal, diuretic, metalloprotease inhibitory and central nervous system activity.[1] Recently, there has been growing interest in the development of solid-phase synthetic approaches to hydantoin derivatives, particularly those substituted at the *N*-1, *N*-3 and *C*-5 positions.[2–10] In contrast to the many examples of the synthesis of hydantoin derivatives on solid-supports, there are only a few reports on the synthesis of 1-aminohydantoins[11] and 3-aminohydantoins.[12,13] To the best of our knowledge, there are no reports on the solid-phase synthesis of 3-aminodihydrouracil and thiodihydrouracil derivatives. In the preceding paper, we reported a one-pot solution-phase synthetic route to 3-aminohydantoin and dihydrouracil derivatives. We describe herein the general solid-phase synthesis of 3-amino-hydantoins, -thiohydantoins, -dihydrouracils and -thiodihydrouracils.

Although our one-pot solution-phase methodology provides a simple route to 3-aminohydantoin and 3-aminodihydrouracil derivatives **I** (Fig. 1), there are some drawbacks related to it: First, the substituent at *N*-1 derives from an α-amino acid derivative and only a limited number of *N*-substituted α-amino acid derivatives is commercially available which limits the potential scope of this method. Secondly, the preparation and purification of compounds with basic substituents such as the *N*-alkylamine substituted 3-aminohydantoin derivatives **II** (Fig. 1) (and their starting materials, namely *N*-alkylamine substituted α-amino acids), is very tedious. In view of this, we deemed it of interest to extend our solution-phase chemistry to a solid-phase method for the preparation of 3-aminohydantoins and dihydrouracils. The synthesis is shown in Scheme 1.

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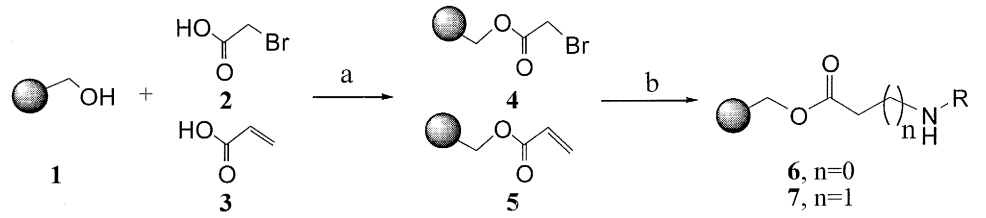
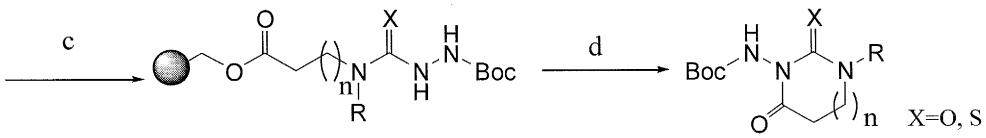
I R = alkyl, Ar
n = 0, 1

II

Fig. 1.



1 **2** **3** **4** **5** **6**, n=0 **7**, n=1



8, n=0
9, n=1

10 (a-s), n=0
11 (a-f), n=1

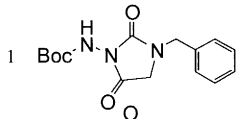
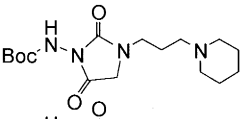
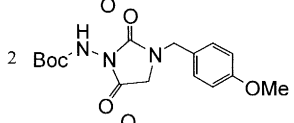
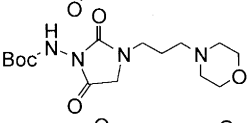
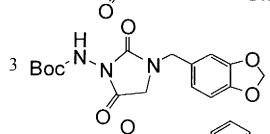
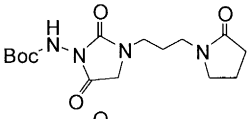
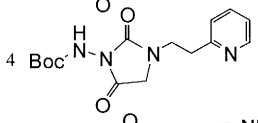
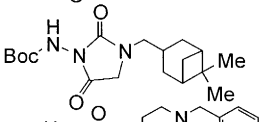
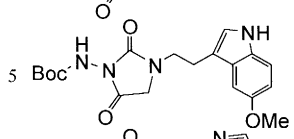
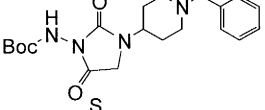
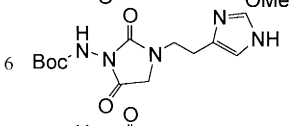
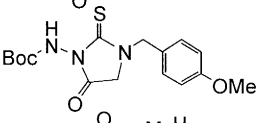
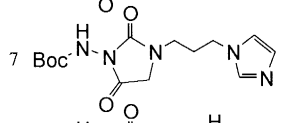
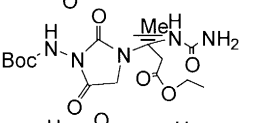
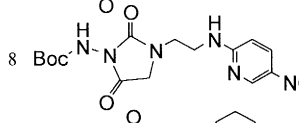
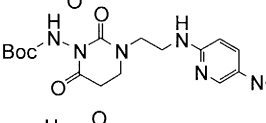
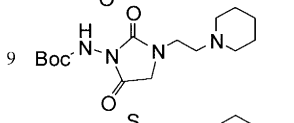
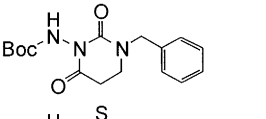
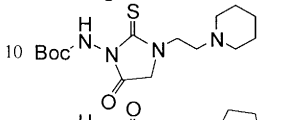
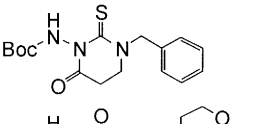
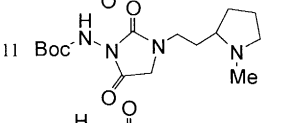
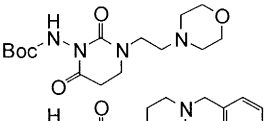
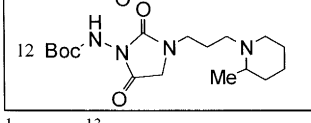
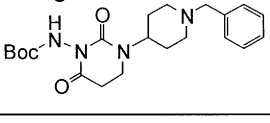
X=O, S

Scheme 1. Reagents: (a) DIC, DMF, 0.1 equivalent DMAP; (b) NH_2-R, DMF or DMSO, rt, 24 h; (c) Boc-NH-NH-CO-Im, DMF, rt, 8–24 h; (d) DMF, 60–90°C, 12–24 h

Esterification of hydroxymethyl polystyrene (Merrifield's resin) **1** with 5–10 equivalents bromoacetic acid **2** or acrylic acid **3** in DMF in the presence of 5–10 equivalents of 1,3-diisopropyl carbodiimide (DIC) and 0.1 equivalents of 4-dimethylaminopyridine (DMAP) gave resin-supported bromoacetic ester **4** or acrylic ester **5**. A suspension of **4** or **5** in DMF (or DMSO for **5**) was treated with 5 equivalents of an alkyl amine at room temperature for 24 h to provide **6** or **7**, respectively.

With compound **6** (R=$C_6H_4CH_2$) in hand, we attempted to use a method similar to the one-pot solution-phase synthesis, in which the coupling of **6** with Boc-hydrazine carbonylimidazole and cyclization were carried out simultaneously. Compound **6** was reacted with 1.5 equivalents of Boc-hydrazine carbonylimidazole (pre-prepared by the addition of *tert*-butyl carbazate to carbonyl diimidazole (CDI) in DMF) at room temperature for 8 h providing only trace amount of the desired product **10** (X=O, by LC-MS and NMR). This lower yield was due to incomplete cyclization. When the reaction was heated to 50°C for 8 h, the product **10** (X=O) was observed but was contaminated with Boc-hydrazine-substituted carbonylimidazole and imidazole. Even after washing with water and 0.1N HCl, the purity of the product was only moderate (LC-MS and NMR). The large reagent excesses used to drive this solid-phase reaction to completion complicates product purification. Hence, we changed to a two-step protocol, in which the coupling and cyclization/cleavage steps were carried out separately. First, the coupling of **6** with excess of Boc-hydrazine carbonylimidazole (5 equivalents) was performed at room temperature to afford resin-bound intermediate **8** which was purified by washing and filtration. Cyclization/cleavage was carried out by heating in DMF at 50°C overnight. This two-step protocol proceeded smoothly to provide final product **10** (R=$C_6H_5CH_2$) in 49% overall chemical yield (four steps). The purity of **10** was improved

Table 1
Solid-phase synthesis of 3-aminohydantoin and dihydrouracil derivatives

Entry	Products[a]		Purity[b]	Yield[c]	Entry	Products[a]		Purity[b]	Yield[c]
1		**10a**	97%	49%	13		**10m**	90%	58%
2		**10b**	95%	54%	14		**10n**	81%	54%
3		**10c**	90%	57%	15		**10o**	74%	45%
4		**10d**	93%	63%	16		**10p**	86%	57%
5		**10e**	96%	61%	17		**10q**	66%	21%
6		**10f**	86%	50%	18		**10r**	90%	32%
7		**10g**	95%	42%	19		**10s**	---	---
8		**10h**	97%	59%	20		**11a**	94%	46%
9		**10i**	98%	59%	21		**11b**	95%	52%
10		**10j**	79%	41%	22		**11c**	90%	22%
11		**10k**	83%	69%	23		**11d**	98%	42%
12		**10l**	86%	67%	24		**11f**	85%	45%

a. ^{1}H and ^{13}C NMR, HRMS and mass spectral data were consistent with the indicated structures. *b*. Purity of products was assayed by HPLC ($H_3PO_4/H_2O/CH_3CN$: 0.1/94.9/5). *c*. Isolated yields were based on the loading of commercial resin **1**.

substantially (>90% by LC-MS and NMR) through a simple filtration and evaporation. Cyclization of 3-aminodihydrouracil derivatives **11** were also successful by heating in DMF at 90°C for 24 h.

Using the protocol[14] described above, we synthesized a variety of 3-aminohydantoin and 3-aminodihydrouracil derivatives. The results are summarized in Table 1.

In most cases, the aromatic and heteroaromatic-substituted primary amines were smoothly coupled and underwent cyclization/cleavage to afford products **10a**–**10h** and **11a**–**11b** in good yield and high purity (entries 1–8, 20, 21). Similarly, incorporation of heterocyclic-substituted amines and alkyl amines were also successful (entries 9–16, 23). Using the same conditions, the 3-aminothiohydantoins and 3-aminodihydrothiouracils were obtained in lower yield (entries 18 and 22). Secondary amines provided products in 21 and 45% yields, respectively (entries 17 and 24). None of the desired product was obtained from a *tert*-alkyl-substituted amine (entry 19).

In summary, an efficient and convenient route to the synthesis of 3-aminohydantoins and dihydrouracils using solid-phase chemistry has been developed. This solid-phase method allows for easy purification of amine-containing compounds and provides for a diverse set of substituents at the 1-position which derive from readily available primary amines.

Acknowledgements

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14. Experimental details for the synthesis of **11a**: (a) Preparation of Merrifield resin-bound acrylate ester **5**: To a solution of 1,3-diisopropyl carbodiimide (15 g, 119 mmol), acrylic acid (17 g, 208 mmol) and Merrifield resin (25 g, 20 mmol, loading level: 0.80 mmol/g) in methylene chloride (300 mL) was added DMAP (0.5 g, 4 mmol). The resulting mixture was shaken at room temperature for 24 h. Resin was collected on a glass filter and washed twice each with DMF, MeOH, DCM. The resin was dried to give the Merrifield resin-bound acrylate ester **5** (37 g, yield 94%). (b) Preparation of compound **11a**: The Merrifield resin-bound acrylate ester **5** (2 g, loading 0.8 mmol/g) was treated with DMSO (50 mL) and 2-(2-aminoethylamino)-5-nitropyridine (1.46 g, 8.0 mmol) and allowed to shake for 24 h at room temperature. Washing twice each with DMF, MeOH, DCM afforded resin **7** (where R=(5-nitro-2-pyridinyl)aminoethyl), which was then treated with Boc-hydrazinecarbonylimidazole (8 mmol) (prepared in situ as described in the preceding paper) in 40 mL of DMF at room

temperature for 24 h and washed twice each with DMF, MeOH, DCM afforded resin **9** (X=O). The resin **9** was placed in a flask with 40 mL of DMF and heated to 95°C for 24 h. After cooling, the resin was filtered, washed with small amounts of DMF, DCM, MeOH and the combined filtrates was concentrated. The residue was dissolved in 40 mL of EtOAc and filtered, concentrated in vacuo to give the desired product **11a** (289 mg, 46%, purity: >95% by LC-MS). MS *m/z* 395 (M+1); ^{1}H NMR ($CDCl_3$) δ 9.02 (d, 1H, *J*=2.6 Hz), 8.16, 8.14 (d×d, 1H, J_1=J_2= 2.8 Hz), 6.69 (s, 1H), 6.48 (d, 1H, *J*=2.6 Hz), 6.04 (br, 1H), 3.77 (m, 4H), 3.61 (m, 1H), 3.46 (m, 1H), 2.85 (m, 2H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 167.5, 165.0, 154.7, 153.9, 144.5, 136.1, 110.0, 83.0, 48.6, 42.8, 41.2, 31.9, 28.4; HRMS calcd for $C_{16}H_{23}N_6O_6$ (M+H): 395.1679; found: 395.1668.