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An efficient one-pot synthesis of 3-aminohydantoin and 3-aminodihydrouracil derivatives

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Abstract

An efficient one-pot synthesis of 3-aminohydantoin and 3-aminodihydrouracil derivatives is described. This methodology provides a simple, straightforward and versatile synthetic route to these interesting classes of heterocycles. © 2000 Elsevier Science Ltd. All rights reserved.

3-Aminohydantoin and 3-aminodihydrouracil derivatives are interesting classes of heterocycles which have demonstrated utility in pharmaceutical and agrochemical research. Compounds containing the 3-aminohydantoin and 3-aminodihydrouracil nucleus have been explored for use as anticonvulsant agents,[1] antibacterial agents,[2,3] metalloprotease inhibitors,[4] diuretic agents[5] and pesticides.[6] Although several reports have been published for the preparation of 3-aminohydantoin derivatives,[1–3,5–16] most of them generally suffer from either multiple synthetic steps, harsh reaction conditions or lack of versatility. Recently, Yoon et al.[17] developed a five-step, four-pot synthesis of 3-aminohydantoins which served as bases for a soluble polymer-supported synthesis. We describe herein an efficient one-pot synthesis of 3-aminohydantoins and thiohydantoins, which is likewise the basis for a polymer-suported synthesis. In addition, we have expanded our methodology to the preparation of the 3-aminodihydrouracils and thiodihydrouracils, the higher homologs of the 3-aminohydantoins. The general procedure is shown in Scheme 1. Successive treatment of carbonyldiimidazole or thiocarbonyldiimidazole (**1**) with *tert*-butyl carbazate (**2**) followed by addition of a variety of α-amino or β-amino acid esters **4** gives the desired final products **6** in modest to very good yield.[18]

We began this study by testing the conversion of *tert*-butyl carbazate (**2**) to intermediate **3**. We initially anticipated that indiscriminate displacement of the imidazolyl moiety of carbonyldiimidazole by *tert*-butyl carbazate (**2**) would give a mixture of mono- and di-substituted products. The results showed, however, that when *tert*-butyl carbazate (**2**) was added slowly to the slight excess of carbonyldiimidazole or thiocarbonyldiimidazole in dioxane at room temperature, the intermediate **3** was formed as the sole product (97%, product was characterized by NMR). Without work-up or purification, the intermediate **3** was sufficiently pure for the next step.

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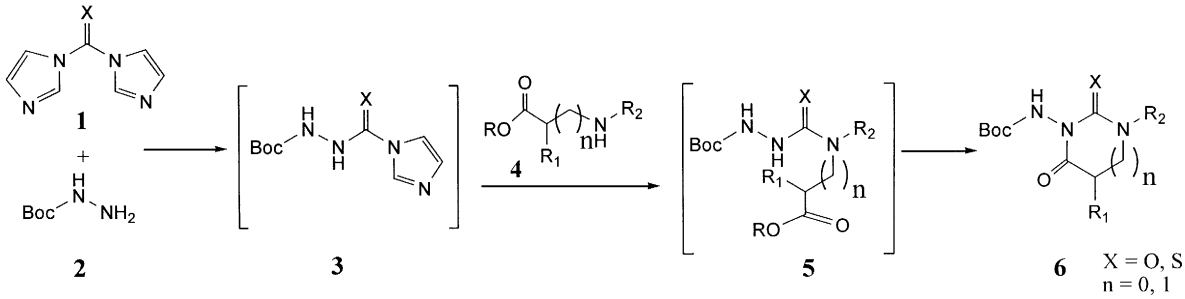


Scheme 1.

We next focused our studies on finding optimal conditions for both the displacement of the imidazolyl moiety of **3** by *N*-substituted amino acid esters and the succeeding cyclization reaction. When the intermediate **3** was treated with *N*-benzylglycine ester (**4**) in dioxane for 8 h at room temperature, only a small amount of cyclization product **6a** was observed. The major product was the uncyclized intermediate **5**. However, when heated to 50–60°C, the cyclization was complete within 4 h in very good yield. Notably, the impurities in this reaction could be removed by a simple liquid/liquid extraction providing the desired product **6a** in high purity (>95%).

Examination of solvent effects revealed that commonly used solvents, such as THF, DMF or dioxane were of approximately equal effectiveness, providing **6a** in very good chemical yields (94, 92 and 95%). Methylene chloride and acetonitrile gave slightly lower yields (85 and 88%). The different ester groups, such as the methyl, ethyl and benzyl groups, are essentially equivalent for the cyclization.

Results for the synthesis of a variety of 3-aminohydantoin/thiohydantoin derivatives, **6a**–**6o**, using these optimized conditions are summarized in Table 1. Intermediate **3** reacts with *N*-benzylglycine or alanine esters to give products **6a**–**6d** in high yield (entries 1–4). Similarly, chiral and racemic cyclic amino acid esters as well as heterocyclic amino acid esters were smoothly converted into the corresponding bicyclic or tricyclic products **6e**–**6l** (entries 5–12). The X-ray crystal structure of **6i** (Fig. 1) verified the predicted structure and stereochemistry as well as intermolecular hydrogen bonding in the solid state. (*R*)-4-Hydroxy-L-proline ester gave **6m** in relatively lower yield (43%, entry 13), perhaps due to the increased water solubility of the product leading to losses during work-up. Under the same conditions, a longer reaction time (10 h) was required for the high yield conversion of *N*-phenylglycine ethyl ester to the desired products **6n**–**6o** (entries 14–15).

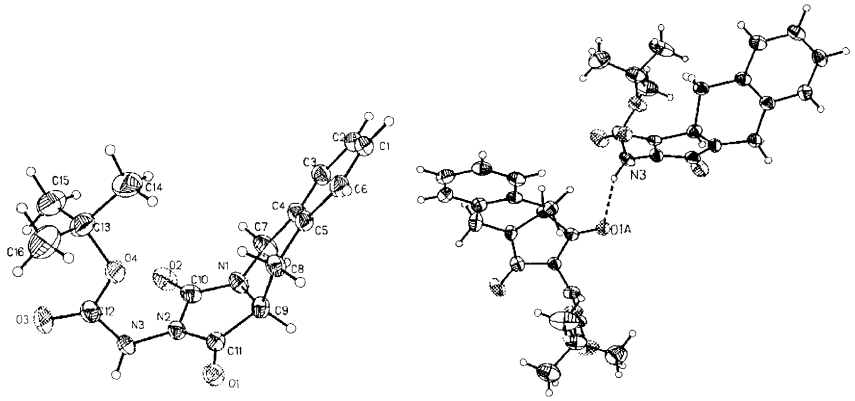
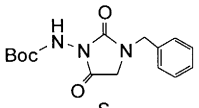
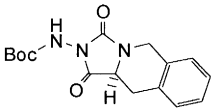
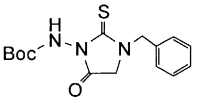
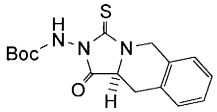
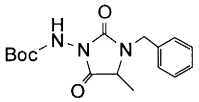
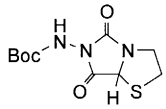
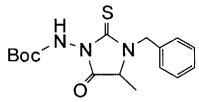
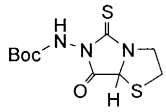
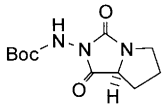
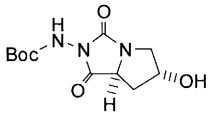
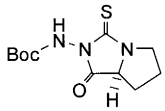
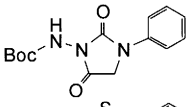
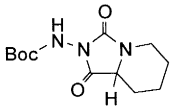
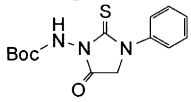
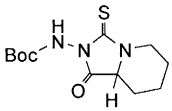


Fig. 1. X-Ray crystal structure of **6i**

Table 1
One-pot synthesis of 3-aminohydantoin/thiohydantoin derivatives

Entry	Product		Yield[a]	Entry	Product		Yield[a]
1		**6a**	95%	9		**6i**	87%
2		**6b**	95%	10		**6j**	94%
3		**6c**	81%[b]	11		**6k**	74%
4		**6d**	80%	12		**6l**	82%[b]
5		**6e**	91%	13		**6m**	43%
6		**6f**	92%	14		**6n**	76%
7		**6g**	90%	15		**6o**	81%
8		**6h**	93%				

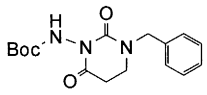
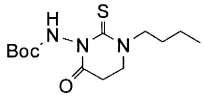
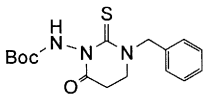
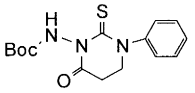
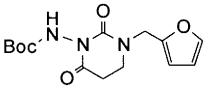
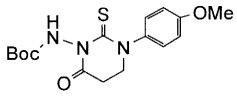
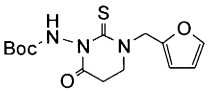
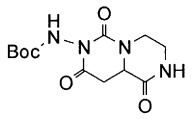
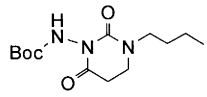
a. Isolated yields. ^{1}H and ^{13}C NMR, mass spectral data and elemental analyses were consistent with the indicated structures without chromatographic purification. Product **6o** was characterized after chromatographic purification. *b*. Purity of **6c** was 86% and **6l** was 82% by HPLC ($H_3PO_4/H_2O/CH_3CN$: 0.1/94.9/5).

This methodology was extended to the preparation of a series of novel 3-amino-1-substituted dihydrouracils/dihydrothiouracils from the corresponding *N*-substituted β-amino acid esters. Compared to hydantoin ring formation, cyclization to the dihydrouracil ring was sluggish at 60°C. However, when the reactions were carried out at 100°C and longer times (>15 h), the cyclization proceeded smoothly. Only desired products were observed in most cases (Table 2).

As shown in Table 2, the *N*-benzyl and *N*-furfuryl, as well as *N*-*n*-butyl substituted β-amino acid esters, afforded the desired products **6p**–**6u** in good yield (entries 1–6). The *N*-phenyl and *N*-*p*-methoxyphenyl-substituted β-amino acid esters, however, provided **6v** and **6w** in lower yield (entries 7 and 8). The major products obtained in these two reactions were non-cyclized products. When ethyl 3-oxopiperazine 2-acetate was used, the bicyclic products **6x** was obtained in good yield (entry 9).

In summary, an efficient one-pot synthesis of 3-aminohydantoin and 3-aminodihydrouracil derivatives has been developed. This method is simple (one-pot) with mild reaction conditions, and provides high

Table 2
One-pot synthesis of 3-aminodihydrouracil/dihydrothiouracil derivatives

Entry	Product		Yield[a]	Entry	Product		Yield[a]
1		**6p**	64%	6		**6u**	81%
2		**6q**	72%	7		**6v**	33%[b]
3		**6r**	65%	8		**6w**	35%
4		**6s**	77%	9		**6x**	78%
5		**6t**	84%				

a. Isolated yields. ^{1}H and ^{13}C NMR, mass spectral data and elemental analyses were consistent with the indicated structures after chromatographic purification. *b*. Purity of **6v** was 84% by HPLC ($H_3PO_4/H_2O/CH_3CN$: 0.1/94.9/5).

yields without purification in most 3-aminohydantoin cases. In addition, this method provides a versatile synthetic route to 3-aminohydantoin, thiohydantoin and 3-aminodihydrouracil, thiodihydrouracil derivatives from commercially available starting materials.

Acknowledgements

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18. Experimental details for the synthesis of **6i**: To a solution of 1.08 g (6 mmol) of carbonyldiimidazole (**1**) in 25 mL of 1,4-dioxane was added dropwise 0.66 g (5 mmol) of *tert*-butyl carbazate (**2**) in 25 mL of 1,4-dioxane. The solution was stirred for 3 h at room temperature, followed by the addition of benzyl (*S*)-(−)-1,2,3,4-tetrahydro-3-isoquinoline carboxylate *p*-toluenesulfonic acid salt 2.19 g (5 mmol) and triethylamine (0.5 mL). The resulting mixture was heated to 60°C for 4 h. The dioxane was removed under reduced pressure. The residue was dissolved in EtOAc (150 mL) and washed with water (2×50 mL), 0.1N aqueous HCl (2×50 mL), dried with $MgSO_4$ and concentrated to 20 mL in vacuo to give a white precipitate. The solid was filtered off and dried in vacuo to afford **6i** (1.38 g, 87%). ^{1}H NMR ($CDCl_3$) δ 7.18–7.32 (m, 4H), 6.66 (s, 1H), 5.07 (d, 1H, *J*=16.8 Hz), 4.46 (d, 1H, *J*=16.6 Hz), 4.20 (m, 1H), 3.33 (d×d, 1H, J_1=4.5 Hz, J_2=15.7 Hz), 3.02 (m, 1H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.5, 154.0, 153.1, 130.7, 129.6, 127.7, 127.5, 126.8, 83.4, 53.8, 41.9, 30.9, 28.2; MS *m/z* 318 (M+1); anal. calcd $C_{16}H_{19}N_3O_4.0.2\ H_2O$: C, 59.88; H, 6.09; N, 13.09. Found: C, 59.86; H, 5.84; N, 13.00.