

# Solution- and solid-phase synthesis of novel hydantoin and isoxazoline-containing heterocycles

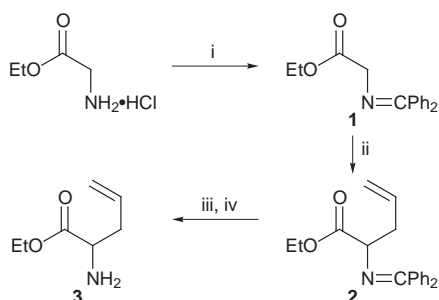
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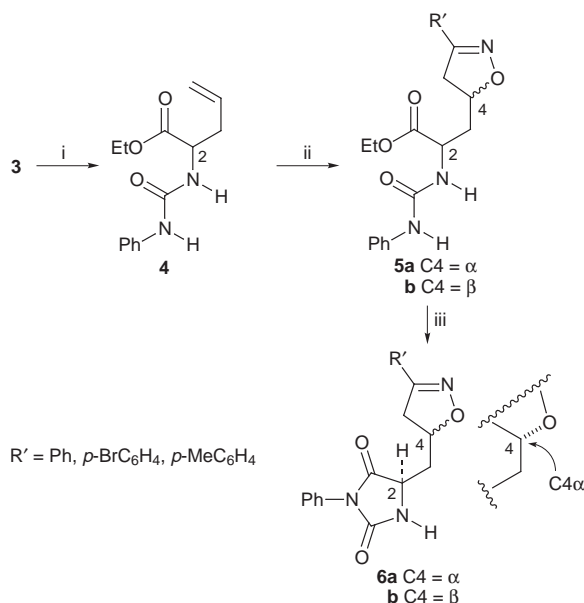
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Exploiting 1,3-dipolar cycloaddition and carbanilide cyclization transformations, novel isoxazolymethylimidazolidinedione heterocycles have been prepared using both solution- and solid-phase methods.

The hydantoin moiety has important medicinal<sup>1</sup> as well as agrochemical<sup>2,3</sup> activities and a large number of hydantoins have been synthesized for various biological applications.<sup>4</sup> Moreover, the isoxazoline heterocycle has been used extensively to modulate various other biologically active motifs.<sup>5</sup> As part of our efforts toward the preparation and biological evaluation of novel hydantoin-containing heterocycles, we disclose here a useful route for the synthesis of isoxazoline-containing hydantoins<sup>6</sup> as well as present a synthetic strategy applicable to solid-phase combinatorial approaches.



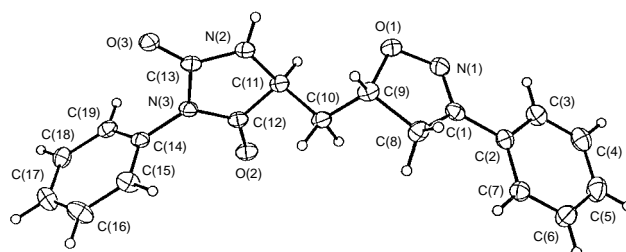
**Scheme 1** Reagents and conditions: i,  $\text{HN}=\text{CPh}_2$ ,  $\text{CH}_2\text{Cl}_2$ , room temp.; ii, allyl bromide, NaH, DMF, room temp.; iii, HCl (1 M); iv, NaOH (1 M)



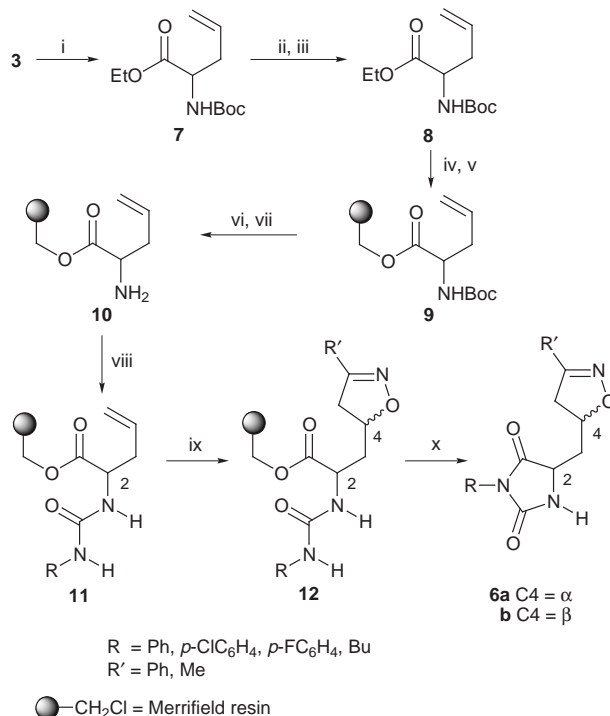
**Scheme 2** Reagents and conditions: i,  $\text{PhN}=\text{C}=\text{O}$ ,  $\text{CH}_2\text{Cl}_2$ , room temp.; ii,  $\text{R}'\text{CH}_2\text{NO}_2$ ,  $\text{PhN}=\text{C}=\text{O}$ ,  $\text{Et}_3\text{N}$ , THF, 60 °C; iii, NaOEt, EtOH, room temp.

The condensation of glycine ethyl ester HCl salt with benzophenone imine gave benzophenone Schiff base **17** (5 mmol scale, 95% yield) which was alkylated with allyl bromide to give protected amino ester **2** (5 mmol scale, 90% yield) (Scheme 1). Hydrolysis of the imine moiety in **2** with aq. HCl and subsequent neutralization of the resulting ammonium salt with aq. NaOH delivered **3** (5 mmol scale, 86%).

The free amine of **3** was reacted with phenyl isocyanate in  $\text{CH}_2\text{Cl}_2$  at ambient temperature for 2 h to give urea **4** in 90% yield (5 mmol scale) (Scheme 2). 1,3 Dipolar cycloaddition to the alkene in **4** with a Mukaiyama-generated nitrile oxide<sup>8</sup> gave isoxazoline heterocycle **5**<sup>9</sup> as a C4 $\alpha$  and C4 $\beta$  mixture of



**Fig. 1** Crystallographic projection of **6a** ( $\text{R} = \text{Ph}$ )



**Scheme 3** Reagents and conditions: i,  $\text{Boc}_2\text{O}$ ,  $\text{CH}_2\text{Cl}_2$ , reflux; ii, NaOH (1 M); iii, HCl (1 M); iv, KOH; v, 18-crown-6, Merrifield resin, DMF, 70 °C; vi, TFA,  $\text{CH}_2\text{Cl}_2$ ; vii,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ; viii,  $\text{RN}=\text{C}=\text{O}$ ,  $\text{CH}_2\text{Cl}_2$ , room temp.; ix,  $\text{R}'\text{CH}_2\text{NO}_2$ ,  $\text{PhN}=\text{C}=\text{O}$ ,  $\text{Et}_3\text{N}$ , THF, 60 °C; x,  $\text{Et}_3\text{N}$ , THF, 60 °C

diastereomers (4 mmol scale, **5a**:**5b**:1:1 ratio, yield 60–70%). While separable by flash-column chromatography, each diastereomer of **5** gave the same mixture of two diastereomeric isoxazoloimidazolidinediones **6** upon treatment with NaOEt (1.0 equiv.) in EtOH. Due to this propensity for C2 epimerization during the carbanilide cyclization (**5a**→**6a** + **6b** or **5b**→**6a** + **6b**; 4 mmol scale; **6a**:**6b**:1:1; 80% yield), it was in fact most expedient to effect this transformation on the **5a/5b** mixture. X-Ray crystallographic analysis§ of **6a** (R = Ph) (Fig. 1) verified the relative stereochemistries of **5a/5b** and **6a/6b**.

Our solid-phase approach<sup>10</sup> to isoxazolylmethylimidazolidinedione **6** began with amino ester **3**, which was Boc-protected to give **7** (4 mmol scale, 95% yield) (Scheme 3). Saponification delivered **8** (4 mmol scale, 90% yield) which was coupled with Merrifield resin to give resin **9**.<sup>11</sup> TFA-mediated removal of the Boc protecting group followed by a resin wash with Et<sub>3</sub>N–CH<sub>2</sub>Cl<sub>2</sub> delivered **10**, the solid-phase analog of **3**. Paralleling the solution results, isocyanate treatment of **10** gave urea **11** and subsequent 1,3-dipolar cycloaddition with a Mukaiyama-generated nitrile oxide gave **12**. A ca. 1:1 mixture of isoxazolylmethylimidazolidinedione diastereomers (**6a/6b**) was obtained on cyclative release.

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## Notes and References

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§ Crystal data: for **6a** (R = Ph): C<sub>19</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>, colorless crystals, *M* = 335.36, orthorhombic, space group *Pbca*, *a* = 9.0062(11), *b* = 11.1037(10), *c* = 32.472(3) Å, *U* = 3247.3(6) Å<sup>3</sup>, *Z* = 8, *D*<sub>c</sub> = 1.372 Mg m<sup>-3</sup>, *μ* = 0.776 mm<sup>-1</sup>, *R* = 0.0392, *wR* = 0.0955, GOF = 1.092, *T* = 130(2) K, *F*(000) = 1408, 2189 independent reflections were collected on a Syntex P2<sub>1</sub> diffractometer using graphite-monochromated Cu-Kα radiation. CCDC 182/917.

¶ Typical procedure for solid-phase isoxazolylmethylimidazolidinedione synthesis: Boc-protected glycine acid **8** (130 mg, 0.6 mmol) was neutralized (room temp., 1 h) with KOH (1.0 equiv., 0.6 mmol) in EtOH–H<sub>2</sub>O (2:1) and, after removing the solvent and drying *in vacuo*, the potassium salt was dissolved in DMF (20 ml) and reacted with Merrifield resin (300 mg, 0.3 mmol; loading ca. 1 mmol Cl g<sup>-1</sup>) and 18-crown-6 (158 mg, 0.6 mmol). The resulting mixture was stirred at 70 °C for 40 h and then washed with DMF (20 ml), THF (20 ml), THF–H<sub>2</sub>O (20 ml × 2), and THF (20 ml). Dried resin **9** (*v*<sub>max</sub>/cm<sup>-1</sup> 1723) was treated with 50% TFA–CH<sub>2</sub>Cl<sub>2</sub> (20 ml) at ambient temperature for 1 h, after which time the resin was washed with CH<sub>2</sub>Cl<sub>2</sub> (20 ml), dioxane (20 ml) and CH<sub>2</sub>Cl<sub>2</sub> (20 ml × 2). An Et<sub>3</sub>N wash (10% in CH<sub>2</sub>Cl<sub>2</sub>, 20 ml) followed by CH<sub>2</sub>Cl<sub>2</sub> washes (20 ml × 2) gave resin **10** (*v*<sub>max</sub>/cm<sup>-1</sup> 3383, 1735). Phenyl isocyanate (107 mg, 0.9 mmol) in

CH<sub>2</sub>Cl<sub>2</sub> (20 ml) was added and, after 10 h at ambient temperature, the resin was washed with DMF (20 ml), THF (20 ml) and CH<sub>2</sub>Cl<sub>2</sub> (20 ml) and dried to give resin **11** (R = Ph; *v*<sub>max</sub>/cm<sup>-1</sup> 1740, 1700, 1662). α-Nitrotoluene (123 mg, 0.9 mmol), phenyl isocyanate (214 mg, 1.8 mmol) and Et<sub>3</sub>N (10 μl) were added to this resin in THF (20 ml). After incubating at 60 °C for 20 h, washing the resin with DMF (20 ml), THF (20 ml) and CH<sub>2</sub>Cl<sub>2</sub> (20 ml) gave resin **12** (R = R' = Ph; *v*<sub>max</sub>/cm<sup>-1</sup> 1738, 1699) which was finally treated with Et<sub>3</sub>N (1 ml) in THF (20 ml) at 60 °C for 20 h. Resin was removed from the liberated product to give **6a/6b** (R = R' = Ph) in 35% overall yield from Merrifield resin. These two isomers were easily separated by flash chromatography (EtOAc–hexane 1:2) to give **6a** (R = R' = Ph; 16 mg, 16% overall yield) and **6b** (R = R' = Ph; 19 mg, 19% overall yield). The optimized solid-phase overall yield of **6a** + **6b** is 35%, which translates to ca. 84% yield per step from **8**. With catalytic Et<sub>3</sub>N, we saw no evidence for formation of **6** in **11**→**12**.

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