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

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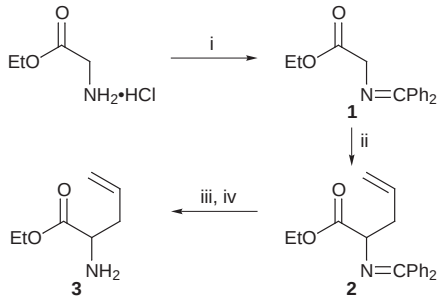
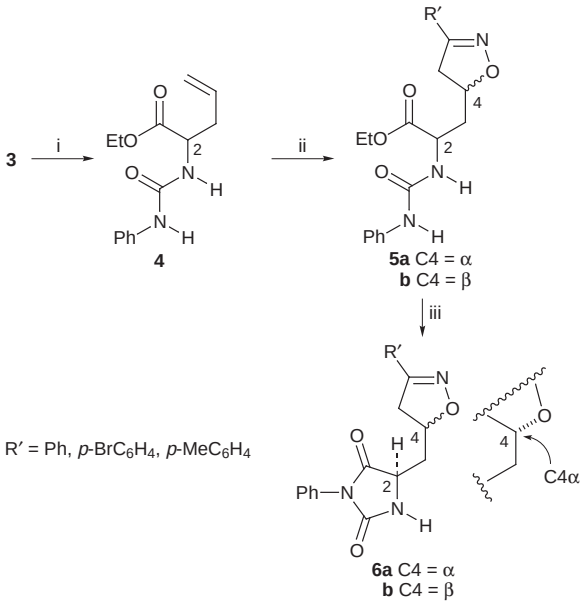
Exploiting 1,3-dipolar cycloaddition and carbanilide cyclization transformations, novel isoxazolylmethylimidazolidinedione heterocycles have been prepared using both solution- and solid-phase methods.

The hydantoin moiety has important medicinal[1] as well as agrochemical[2,3] activities and a large number of hydantoins have been synthesized for various biological applications.[4] Moreover, the isoxazoline heterocycle has been used extensively to modulate various other biologically active motifs.[5] 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[6] as well as present a synthetic strategy applicable to solid-phase combinatorial approaches.



Scheme 1 *Reagents and conditions*: i, $HN{=}CPh_2$, CH_2Cl_2, room temp., ii, allyl bromide, NaH, DMF, room temp.; iii, HCl (1 M); iv, NaOH (1 M)



Scheme 2 *Reagents and conditions*: i, PhN=C=O, CH_2Cl_2, room temp.; ii, RCH_2NO_2, PhN=C=O, Et_3N, THF, 60 °C; iii, NaOEt, EtOH, room temp.

The condensation of glycine ethyl ester HCl salt with benzophenone imine gave benzophenone Schiff base **1**[7] (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 CH_2Cl_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[8] gave isoxazoline heterocycle **5**[9] as a C4α and C4β mixture of

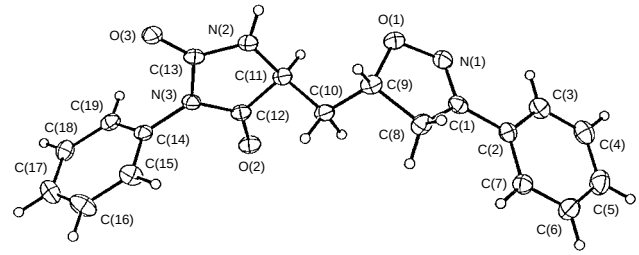
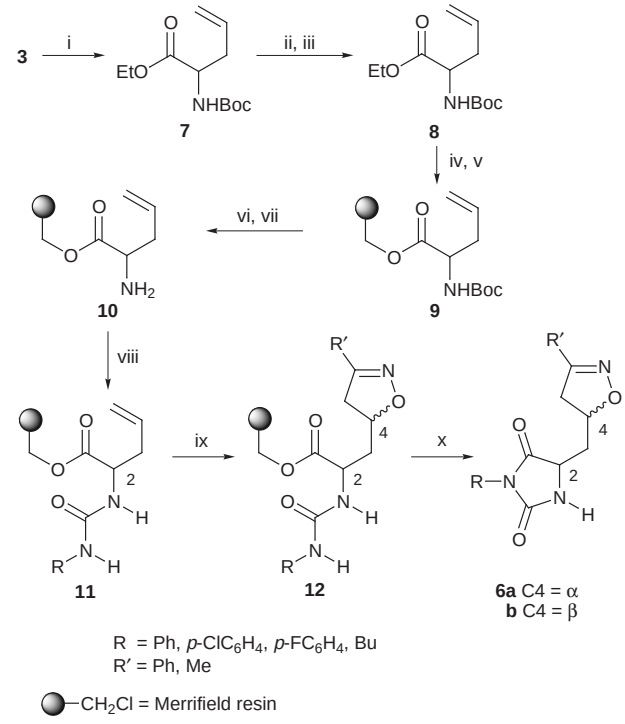


Fig. 1 Crystallographic projection of 6a (R = Ph)



Scheme 3 *Reagents and conditions*: i, Boc_2O, CH_2Cl_2, reflux; ii, NaOH (1 M); iii, HCl (1 M); iv, KOH; v, 18-crown-6, Merrifield resin, DMF, 70 °C; vi, TFA, CH_2Cl_2; vii, Et_3N, CH_2Cl_2; viii, RN=C=O, CH_2Cl_2, room temp.; ix, $R'CH_2NO_2$, PhN=C=O, Et_3N, THF, 60 °C; x, Et_3N, 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[10] 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.**[11]¶ TFA-mediated removal of the Boc protecting group followed by a resin wash with Et_3N–CH_2Cl_2 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): $C_{19}H_{17}N_3O_3$, 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^3, Z = 8, D_c = 1.372 Mg m^{-3}, μ = 0.776 mm^{-1}, R = 0.0392, wR = 0.0955, GOF = 1.092, T = 130(2) K, F(000) = 1408, 2189 independent reflections were collected on a Syntex $P2_1$ 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_2O (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^{-1}) 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_2O (20 ml× 2), and THF (20 ml). Dried resin **9** (ν_{max}/cm^{-1} 1723) was treated with 50% TFA–CH_2Cl_2 (20 ml) at ambient temperature for 1 h, after which time the resin was washed with CH_2Cl_2 (20 ml), dioxane (20 ml) and CH_2Cl_2 (20 ml× 2). An Et_3N wash (10% in CH_2Cl_2, 20 ml) followed by CH_2Cl_2 washes (20 ml× 2) gave resin **10** (ν_{max}/cm^{-1} 3383, 1735). Phenyl isocyanate (107 mg, 0.9 mmol) in CH_2Cl_2 (20 ml) was added and, after 10 h at ambient temperature, the resin was washed with DMF (20 ml), THF (20 ml) and CH_2Cl_2 (20 ml) and dried to give resin **11** (R = Ph; ν_{max}/cm^{-1} 1740, 1700, 1662). α-Nitrotoluene (123 mg, 0.9 mmol), phenyl isocyanate (214 mg, 1.8 mmol) and Et_3N (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_2Cl_2 (20 ml) gave resin **12** (R = R′ = Ph; ν_{max}/cm^{-1} 1738, 1699) which was finally treated with Et_3N (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_3N, we saw no evidence for formation of **6** in **11**→**12**.

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