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An uncatalyzed cyclo-elimination process for the release of N_3-alkylated hydantoins from solid-phase: synthesis of novel isoxazoloimidazolidinediones

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Abstract

Solid-phase regioselective nitrile oxide 1,3-dipolar cycloaddition to an ω-alkynyl ester followed by reductive α-*N*-alkylation and isocyanate α-*N*-acylation delivers **I** and sets the stage for the uncatalyzed carbanilide cyclo-elimination of isoxazoloimidazolidinedione heterocycles (**I** → **II**). This traceless release step is induced by simply warming the urea ester intermediate, but requires that the *N*3 of the nascent hydantoin be fully substituted (**I** → **II**; $R_c \neq H$).

The hydantoin moiety plays an important role in medicinal[1] as well as agrochemical[2,3] activities and the isoxazole heterocycle has been used to modulate the biological activity of various other motifs.[4] As part of our efforts toward the preparation and biological evaluation of novel hydantoin containing heterocycles, we disclose here an efficient route for the synthesis of novel isoxazole-containing hydantoins (i.e., isoxazoloimidazolidinedione heterocycles **12**) as well as present a synthetic strategy applicable to solid-phase combinatorial approaches.

To date, reports of resin release of hydantoins by cyclo-elimination have required either the use of acid[5] or base[6a–c] catalysis at elevated temperatures or the use of excess base[7] (often as solvent) at ambient temperatures [Scheme 1; (i) and (ii)]. These acid or base requirements can complicate product isolation and often result in lower yield and reduced purity of the final product. Here, we report that the traceless release of *N*3-alkylated hydantoins like **12** can be achieved without any acid or base catalysis [Scheme 1; (iii)].

In our hands, THF suspensions of α-*N*-alkyl substituted urea esters (**I**; R_c=alkyl) undergo cyclo-elimination yielding **II** upon gentle warming (60°C). Acid or base catalysis is not required for this conversion, presumably because the α-*N*-alkyl group accelerates heterocyclization through a buttressing effect. In addition to streamlined workup and product isolation, this thermal approach to product release

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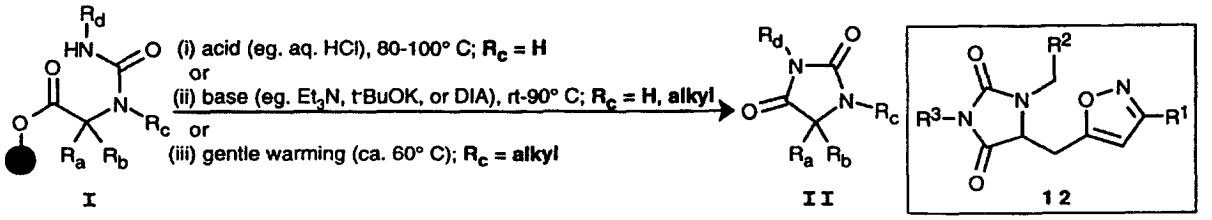
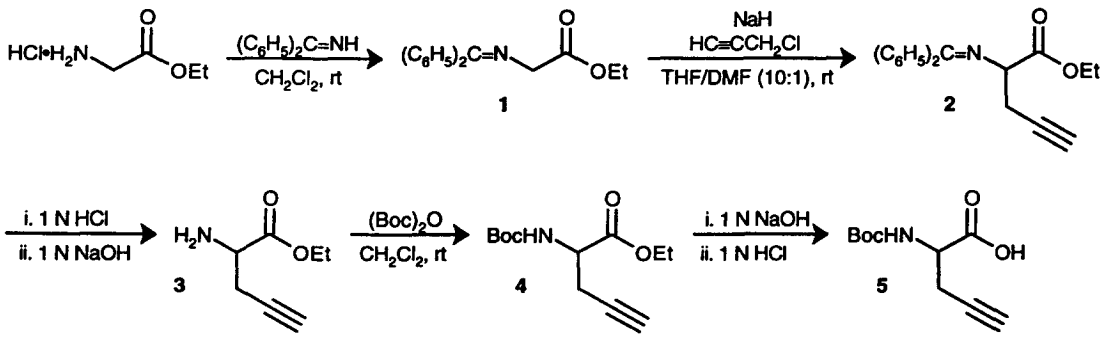


Scheme 1.

affords an advantage in compound purity in that only *N*3-alkylated hydantoins (**II**; R_c=alkyl) are released as α-*N*-unalkylated urea esters (**I**; R_c=H) remain resin bound at 60°C in THF.

We have exploited this novel hydantoin forming itinerary in the preparation of isoxazoloimidazolidinedione heterocycles (**12**). Our solid-phase approach to **12** began with the preparation of Boc-protected amino acid **5** as depicted in Scheme 2.

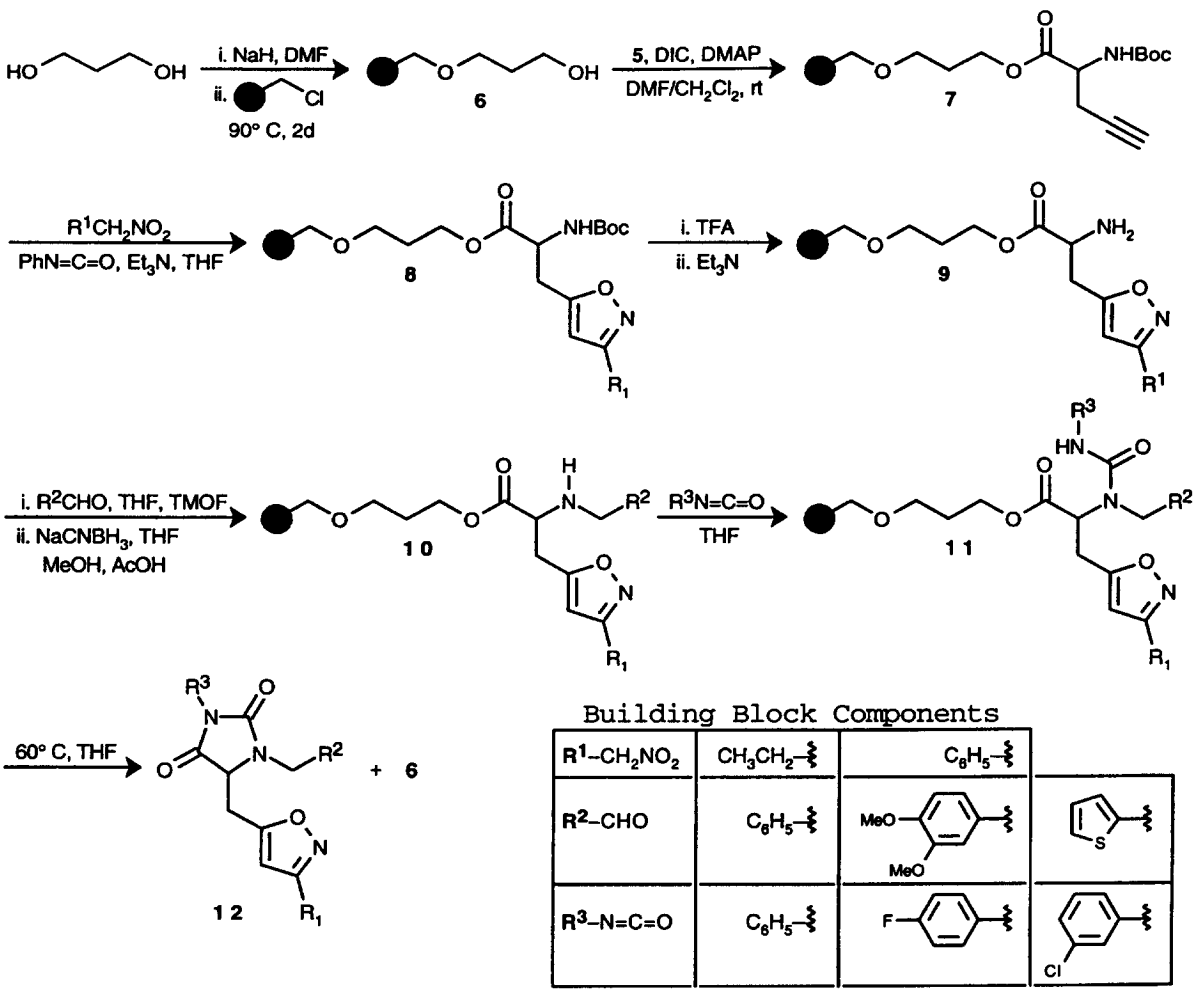


Scheme 2.

Condensation of glycine ethyl ester·HCl with benzophenone imine gave benzophenone Schiff base **1**[8] (5 mmol scale, 95% yield) which was alkylated with propargyl chloride to give protected aminoester **2** (5 mmol scale, 90% yield). Subsequent hydrolysis of the imine moiety in **2** with aqueous HCl followed by neutralization of the resulting ammonium salt with aqueous NaOH delivered **3** (5 mmol scale, 66%). Boc-protection of **3** delivered **4** (4 mmol scale, 95% yield) and saponification and neutralization produced Boc-protected amino acid **5** (4 mmol scale, 90% yield). This carboxylic acid was coupled to Merrifield resin derivative **6**[9] (loading=2 mmol OH/gram) so that subsequent solid-phase reactions would not be hindered by the polymer network (Scheme 3). This coupling was accomplished by treatment of **5** and **6** with DIC.

At this point, a solid-phase 1,3 dipolar cycloaddition[10] reaction of the ω-alkyne moiety in **7** with a Mukaiyama-generated nitrile oxide[11] delivered resin **8**. Deprotection of amino moiety (TFA/CH_2Cl_2) and neutralization (Et_3N) of the resin delivered amino ester **9**. A two-step reductive alkylation of the amino moiety in **9** with aldehydes [$(MeO)_3CH$ in THF] and $NaCNBH_3$ (THF, MeOH, HOAc) gave resin **10**. Treatment of this intermediate with isocyanates gave the urea ester intermediate **11** which released the isoxazole-containing hydantoin **12** by simply heating at 60°C for 1–12 h.[12] The building block components used in this study (R^1-CH_2NO_2, R^2-CHO, R^3-N=C=O) are presented in Scheme 3 and led to the construction of an 18-member array of single isoxazoloimidazolidinediones. Each compound was obtained in 20–35% overall yield from Merrifield resin, appeared as a single spot by TLC, and was >95% pure as judged by ^1H NMR.[13]

In summary, we have prepared novel isoxazole-containing hydantoin heterocycles via solid phase



Scheme 3.

organic synthesis. The key cyclo-elimination step is traceless and occurs by gentle warming of the α-*N*-alkylated urea ester intermediate to deliver isoxazoloimidazolidinedione heterocycles (i.e., **12**).

Acknowledgements

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12. Depending upon substituents, cyclo-elimination occurs slowly even at room temperature.
13. All new compounds were fully characterized.