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Connective synthesis of 5,5-disubstituted hydantoins by tandem α -amination and α -arylation of silyl ketene acetals†

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5,5-Disubstituted hydantoins, formally the cyclisation products of quaternary amino acids, were formed connectively from simple ester-derived starting materials by a one-pot tandem method. Amination of the silyl ketene acetal derivative of a methyl ester takes place by silver-catalysed addition to the N=N bond of an azocarboxamide, generating a *N*-amino-*N'*-aryl urea derivative of a substituted aminoester. Treatment with a base forms an ester enolate which undergoes arylation by intramolecular migration of an aryl ring to the α -position of the ester. The product undergoes ring closure to a hydantoin, which may itself be deprotected and functionalised. Aryl migration is successful with rings of various electronic character and with esters bearing functionalised and unfunctionalised chains, and the products have features in common with several bioactive compounds.

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Introduction

Hydantoin rings, formally the cyclocarbonylation products of amino acids, are found in a number of medically significant molecules (Fig. 1).^{1,2} For example the sodium salts of phenytoin and fosphenytoin have anticonvulsant and antiarrhythmic properties;^{3a} nitrofurantoin is an antibacterial drug;^{3b,c} nilutamide is an androgen receptor antagonist for the treatment of advanced prostate cancer;⁴ dantrolene is used as a muscle relaxant and to prevent malignant hyperthermia.⁵ Substituted hydantoins are furthermore valuable intermediates in the synthesis of amino acids using hydantoinases and other related biocatalysts.⁶

Methods for the synthesis of substituted hydantoins⁷ include the classical Urech synthesis,⁸ and the Bucherer–Bergs⁹ and Biltz reactions.¹⁰ Milder transition metal catalysed approaches have been reported, including the Ugi condensation,¹¹ an aminobarbituric acid-hydantoin rearrangement,¹² and reactions of activated carboxylic acids.¹³ Hydantoins have also been made by α -amination of esters using copper catalysts.^{14,15}

We have shown that intramolecular migration of an aryl ring to the α -position of an amino acid-derived urea can provide a general method for making substituted hydantoins¹⁶ in reactions that involve intramolecular nucleophilic aromatic substitution of enolates on even unactivated aromatic rings.¹⁷

However, such methods make use of available amino acid starting materials and are less applicable to the synthesis of molecules containing ‘non-proteinogenic’ side chains. We therefore sought to develop a tandem approach from simple precursors in which the α -amination¹⁸ of an enolate generates a suitable substrate for a tandem intramolecular arylation,¹⁹ leading directly to an α -arylated quaternary hydantoin.²⁰

Our initial plan for a direct route to structurally diverse 5,5-disubstituted hydantoins is illustrated in Scheme 1. We aimed to initiate the hydantoin synthesis with a silver-catalysed regioselective α -amination using an azocarboxamide to generate a urea derivative from which *N'*-aryl migration to the α -position of the resulting ester followed by ring closure would give a hydantoin.

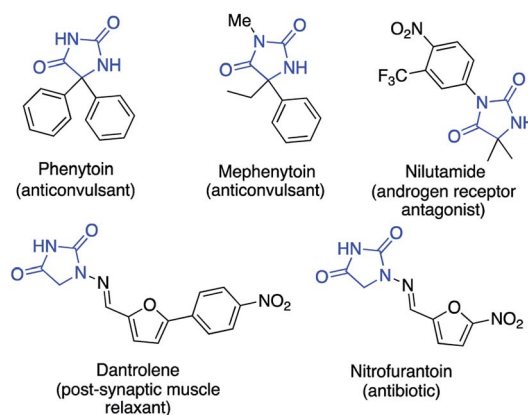
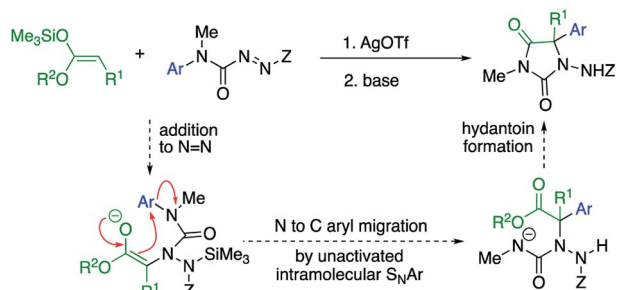


Fig. 1 Examples of drugs containing the hydantoin motif.

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Scheme 1 A route to α -arylated quaternary hydantoins by tandem amination-arylation of silyl ketene acetals. Z = electron-withdrawing group.

Three major challenges need to be overcome. Regioselective addition of the silyl ketene acetal to the azodicarboxamide must lead to a 2-ureido ester to allow the subsequent aryl migration step. Secondly, the enolate of the product must undergo rearrangement rather than any other alternative reaction (such as substitution or elimination), and finally the product must cyclise to a hydantoin. All these steps ideally should occur in a single, tandem process.

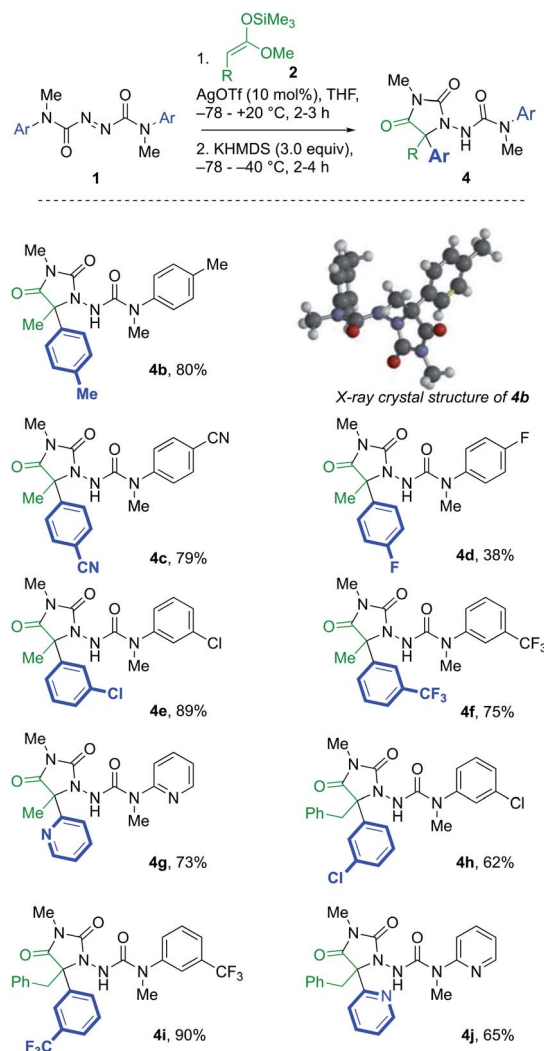
Results and discussion

We started by exploring the amination step with a symmetrical azodicarboxamide to allow us to study the viability of the rearrangement while avoiding issues of regioselectivity. Silver-catalysed aminations of silyl ketene acetals were known using azodicarboxylates,²¹ so azodicarboxamides **1** were made by acylation of hydrazine with *N*-methyl-*N*-arylcabamoyl chloride followed by oxidation with NBS.²² Treatment of a mixture of the azodicarboxamide **1a** and the silyl ketene acetal **2a** with AgOTf (20 mol%) in dichloromethane gave the addition product **3** in 68% yield (Table 1, entry 1). Reducing the catalyst loading to

10 mol% in THF improved this yield to 80% (entry 2). **3** carries an *N'*-aryl urea function suitably located for possible aryl transfer to an enolate derivative. We therefore added 2.0 equiv. KHMDS to the reaction mixture in the hope of promoting this intramolecular arylation. The rearranged product **4a** was obtained in 60% yield, together with 40% of intermediate **3** (entry 3). Increasing the amount of KHMDS to 3.0 equiv. gave clean product **4a** in 75% yield (entry 4).

A further series of azodicarboxamides **1b–g** were made, and likewise treated with silyl ketene acetals **2a** and **2b** (Scheme 2). Hydantoin products **4b–f** were formed successfully bearing electron donating, electron withdrawing groups, and the reaction was successful even with the pyridyl substituted **1g**. Additionally, the structure of the *p*-tolyl derivative **4b** was confirmed by X-ray crystallography.²³ The tandem reaction was also successful with the more hindered silyl ketene acetal **2b** derived from 3-phenylpropionic acids, generating in one pot hydantoins **4h–j** in good yields.

The products **4** all contain a pendent *N*-aryl urea function derived from the second aryl substituent of the symmetrical



Scheme 2 Hydantoin formation from symmetrical azodicarboxamides.

Table 1 Optimising the amination and rearrangement^a

Entry	Reaction conditions	Yields ^b (%)	
		3	4a
1	20 mol% AgOTf, CH ₂ Cl ₂ , -78 → +20 °C, 3 h	68	—
2	10 mol% AgOTf, THF, -78 → +20 °C, 3 h	80 ^c	—
3	(1) 10 mol% AgOTf, THF, -78 → +20 °C, 3 h (2) KHMDS (2.0 equiv.), -78 → -40 °C, 3 h	40	60
4	(1) 10 mol% AgOTf, THF, -78 → +20 °C, 3 h (2) KHMDS (3.0 equiv.), -78 → -40 °C, 3 h	0	75

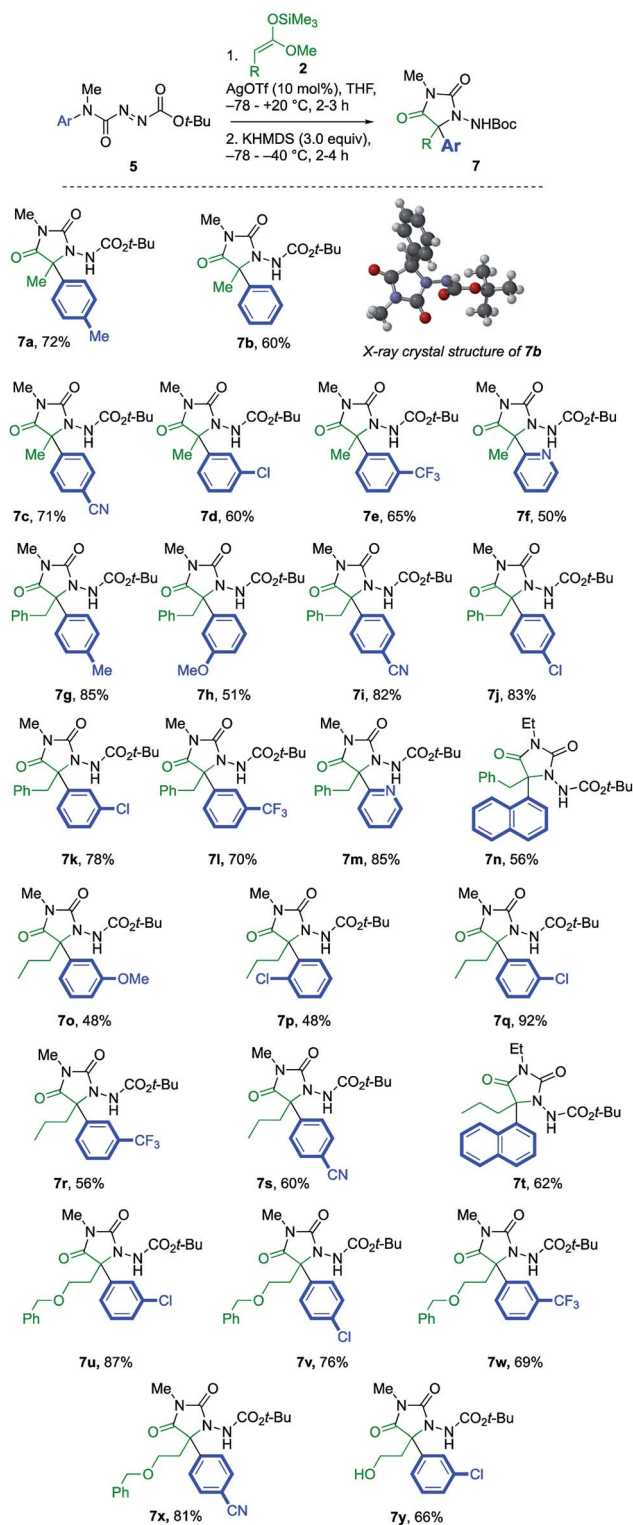
^a Reactions performed using 0.34 mmol of **1a** and 0.34 mmol of **2a** in 3.4 ml solvent. ^b Isolated yield. ^c Similar results obtained with 15 or 20 mol% catalyst.



starting material, and a greater atom economy would be achieved if an alternative unsymmetrical, mono-*N*-arylated azocarboxamide was used as the aminating agent. By treating *N*-methyl-*N*-tolylcarbamoyl chloride with *t*-butyl carbazate, and oxidising the product hydrazide with NBS (see ESI†), we were able to form the azocarboxamides **5**. Treating silyl ketene acetal **2a** with this compound in the presence of 10 mol% AgOTf in CH₂Cl₂ gave the product **6** in 76% yield, accompanied by less than 5% of the alternative regioisomer (Table 2, entry 1). In THF, the yield of **6** increased to 85% and the amination was fully regioselective (entry 2).

When KHMDS was added directly to the crude reaction mixture containing the amination product, arylation and cyclisation to the *N*-Boc-protected aminohydantoin **7a** (entries 3–5) took place, in parallel with the results seen using the symmetrical aminating agent **1a**. With 2.0 equiv. of KHMDS, warming the reaction to –40 °C for 2 h, hydantoin product **7a** was formed in 20% yield (entry 3), increasing to 72% yield on warming to –20 °C (entry 5). Other unsymmetrical aminating agents were also explored, including *N*-benzoyl, *N*-*tert*-butyl-carboxamido and *N*-methyl-*N*-*tert*-butyl carboxamido substituted azo compounds. Although intermediate aminated products corresponding to **6** were obtained, treatment with the base led only to decomposition.

Under these optimised reaction conditions, the generality of the reaction was explored with various azocarboxamides **5** and silyl ketene acetals **2** (Scheme 3). The α -amination of **2a** with a range of azocarboxamides **5** was fully regioselective in all cases. With a simple phenyl ring, the product **7b** was formed in 60% yield and its structure was confirmed by X-ray crystal structure analysis.²³ Electron withdrawing groups *p*-CN, *m*-Cl, and *m*-CF₃ were well tolerated, giving the products **7c–7e** in 65–71% yields. 2-Pyridyl azocarboxamide **5f** likewise performed well and gave hydantoin **7f** in 50% yield.



Scheme 3 A general, connective synthesis of protected *N*-aminohydantoins.

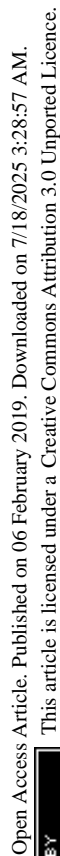
A wider range of alternative silyl ketene acetal partners were explored. 3-Phenylpropionate-derived **2b** provided the hydantoins **7g–i** by migration of either electron-donating or electron-withdrawing rings in 51–85% yields. With a heteroaryl migrating group, the 2-pyridyl azocarboxamide **5f** provided the

Table 2 Optimising the use of unsymmetrical aminating agents^a

Entry	Reaction conditions	Yield ^b (%)	
		6	7a
1	10 mol% AgOTf, CH ₂ Cl ₂ , –78 → +20 °C, 2 h	76 ^c	—
2	10 mol% AgOTf, THF, –78 → +20 °C, 2 h	85	—
3	(1) 10 mol% AgOTf, THF, –78 → +20 °C, 2 h (2) KHMDS (2.0 equiv.), –78 → –40 °C, 2 h	40	20
4	(1) 10 mol% AgOTf, THF, –78 → +20 °C, 2 h (2) KHMDS (3.0 equiv.), –78 → –40 °C, 3 h	0	50
5	(1) 10 mol% AgOTf, THF, –78 → +20 °C, 2 h (2) KHMDS (3.0 equiv.), –78 → –20 °C, 2 h	0	72

^a Reactions performed using 0.36 mmol of **4a**, 0.36 mmol of **2a** in 3.6 ml solvent. ^b Isolated yield. ^c Similar results obtained with 15 or 20 mol% catalyst.





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