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Cascade Reactions |*Hot Paper*|

A Cascade Synthesis of Aminohydantoins Using In Situ-Generated *N*-Substituted Isocyanates

Jean-François Vincent-Rocan, Christian Clavette, Kyle Leckett, and André M. Beauchemin*[a]

Abstract: Nitrogen-substituted isocyanates are rarely utilized but powerful building blocks for the development of cascade reactions in heterocyclic synthesis. These reactive amphoteric intermediates can be accessed in situ via an equilibrium that allows controlled reactivity in the presence of bifunctional partners such as α-amino esters. A cascade reaction has been carried out that forms 3-aminohydantoin derivatives using simple phenoxycarbonyl derivatives of hydrazides and hydrazones as precursors of *N*-substituted-isocyanates. This method allows rapid assembly of complex aminohydantoin derivatives, including analogues of medicinally-relevant compounds, using simple reactants.

Hydantoins are important heterocycles that display a wide range of biological activities. For example, dantrolene (antispasmodic), azimilide (antiarrhythmic), and nitrofurantoin (antibacterial) are valuable pharmaceuticals (Figure 1).[1] A variety of hydantoin syntheses have been described, including cascade reactions from simple starting materials.[1,2] In contrast fewer approaches to aminohydantoin derivatives have been reported,[3] despite their importance as pharmaceuticals and agrochemicals and growing interest in the inclusion of N–N functionalities into molecular scaffolds. Unfortunately, current methods require multistep synthesis and can suffer from chemoselectivity issues that are typically associated with the use of complex hydrazine derivatives.[4] Cascade reactions could provide a streamlined access to this important subunit.

In contrast to normal (*C*-substituted) isocyanates, the reactivity of *N*-substituted isocyanates has received little attention from the synthetic community.[5] Recently, we reported that amphoteric amino- and imino-isocyanates can be formed in situ under mild conditions and engage in high-yielding alkene cycloadditions[6a–c] and nucleophilic additions,[6d,e] despite their known tendency to dimerize or oligomerize.[7,8] Hydrazones[6b–d] and hydrazides[6a,e] are bench-stable, convenient "blocked" *N*-substituted isocyanate precursors[9] that form the desired isocyanates via an equilibrium induced under mild conditions,

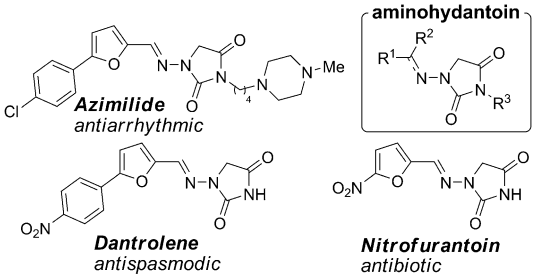
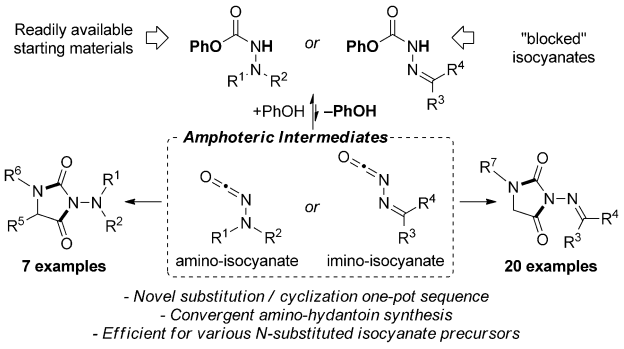


Figure 1. Available therapeutics containing aminohydantoin motifs.

and then react with nucleophiles such as amines, alcohols, and thiols.[6d–e] Using this reactivity, we developed a cascade substitution/hydroamination sequence allowing rapid assembly of saturated nitrogen heterocycles from hydrazide starting materials.[6e] This reactivity showed that amino-isocyanates can engage in controlled cascade reactions forming products bearing the N–N–C=O motif, and hinted that other cascades could be designed. We were drawn to aminohydantoins given their biological activities and the need for more convergent and versatile synthetic approaches. Herein, we report that complex aminohydantoin derivatives are rapidly assembled using a cascade reaction in which both hydrazides and hydrazones are suitable *N*-substituted isocyanate precursors (Scheme 1).



Scheme 1. Cascade reactions exploiting blocked *N*-substituted isocyanates.

Our efforts toward cascade reactions using α-amino esters build on our recent discovery that substitution reactivity on hydrazides proceeds at 60–100 °C [Eq. (1)]. We speculated that this could be optimized, and that, upon heating, cyclization would occur. This cyclization was first observed with a L-proline ester and led to the selective formation of a 5-membered hydantoin over the 6-membered aza-diketopiperazine [Eq. (2)].[10]

[a] *J.-F. Vincent-Rocan, C. Clavette, K. Leckett, Prof. Dr. A. M. Beauchemin*
Centre for Catalysis Research and Innovation
Department of Chemistry, University of Ottawa
10 Marie-Curie, Ottawa, ON K1N 6N5 (Canada)
E-mail: andre.beauchemin@uottawa.ca

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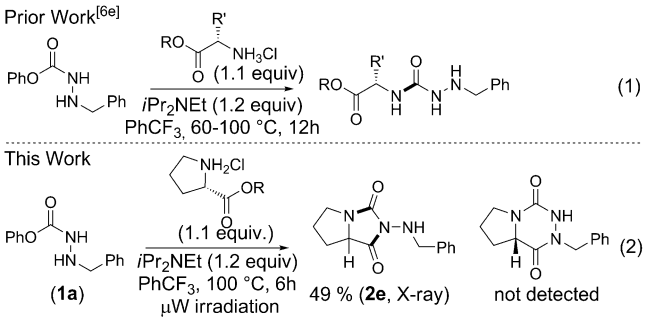
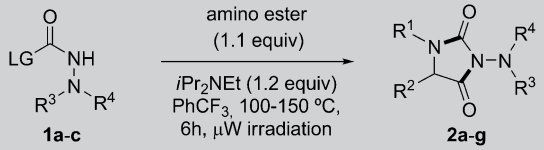


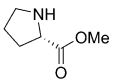
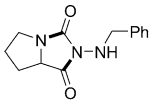
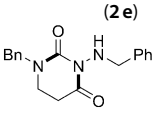
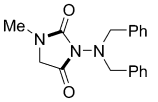
Encouraged by this unoptimized reactivity and high chemoselectivity, we explored the scope of the reaction using simple *N*-benzyl carbazates and α-amino esters (Table 1). We were pleased that *N*-substituted glycine esters formed aminohydantoins in good yields at 100 °C (Table 1, entries 1 and 2), whereas alanine (entry 3), leucine (entry 4) and proline (entry 5) esters also cyclized in moderate to good yields but required higher temperatures, likely due to the conformational preferences[11] of the semicarbazide intermediate. In addition, even a β-amino ester cyclized to yield an amino dihydrouracil derivative (Table 1, entry 6). Finally, *N*,*N*-dibenzylcarbazate **1c** (Table 1, entry 7) also cyclized in good yield. In contrast to the previous examples (LG = OPh; Table 1, entries 1–6), a temperature of 150 °C was required to ensure the formation of the amino-isocyanate intermediate using O*t*Bu as a leaving group.[6a] This leaving group was chosen to facilitate the synthesis of the starting material (**1c**), due to the lability observed during the formation of OPh derivative. It is important to note that cyclizations with enantiopure α-amino esters yield racemic hydantoins, due to their ease of enolization (see the Supporting Information).[4k,m]

Having established the reactivity of hydrazides, we wanted to expand the scope to other *N*-substituted isocyanate precursors. To our knowledge, there have been no examples of cascade reactions involving either imino-isocyanates (C=N–NCO) or amido-isocyanates [C(=O)N–NCO] reported to date, and we felt that this extension would significantly broaden the applicability of this approach to aminohydantoins. Thus we first investigated the ability of imino-isocyanates to engage in cascade reactions, building on our recent report on their substitution reactivity.[6d] We were pleased that several hydrazones used as imino-isocyanate precursors afforded the desired aminohydantoins in the presence of *N*-methyl glycine ethyl ester (Table 2).

Encouragingly, both aliphatic and aromatic hydrazones afforded the desired aminohydantoins (**4a**,**b**,**g** and **4c–f**,**h–i**). The cascade sequence also proceed efficiently using both alde-

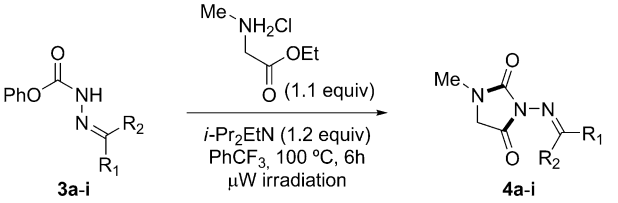
Table 1. Initial scope using *N*-benzyl carbazates and amino esters.[a,b]

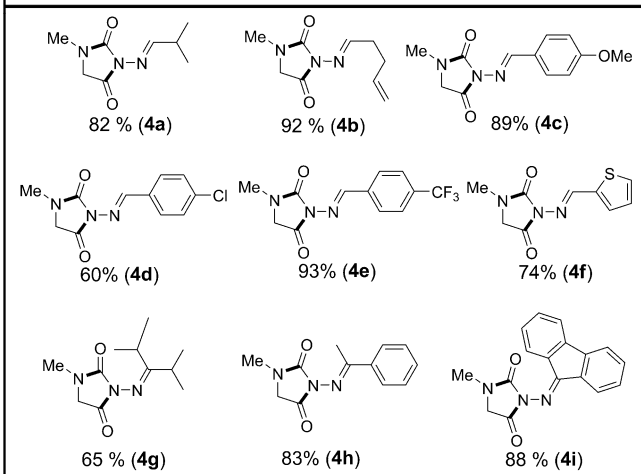


Entry	Amino ester	*T* [°C]	Product	Yield [%]
1	R^1 = Me, R^2 = H, R^5 = Et	100	R^1 = Me, R^2 = H, R^3 = Bn (**2a**)	82
2[c]	R^1 = Bn, R^2 = H, R^5 = Et	100	R^1 = Bn, R^2 = H, R^3 = OMB (**2b**)	72
3	R^1 = H, R^2 = Me, R^5 = Me	150	R^1 = H, R^2 = Me, R^3 = Bn (**2c**)	70
4	R^1 = H, R^2 = *i*Bu, R^5 = Me	150	R^1 = H, R^2 = *i*Bu, R^3 = Bn (**2d**)	62
5		100	 (**2e**)	49
6		150	 (**2f**)	62
7[d]		150	 (**2g**)	81

[a] Conditions: Carbazate (1 equiv), amino ester (1.1 equiv), *i*Pr$_2$NEt (1.2 equiv) in PhCF$_3$ (0.3 M), heated for 6 h (sealed vial, microwave reactor); [b] using *N*-benzyl reagent **1a** (LG = OPh); [c] using *N*-OMB reagent **1b** (LG = OPh); [d] using *N*,*N*-dibenzyl carbazate **1c** (LG = O*t*Bu). LG = leaving group; OMB = *o*-methoxybenzyl.

Table 2. Hydrazone scope using *N*-methyl glycine ethyl ester.[a]



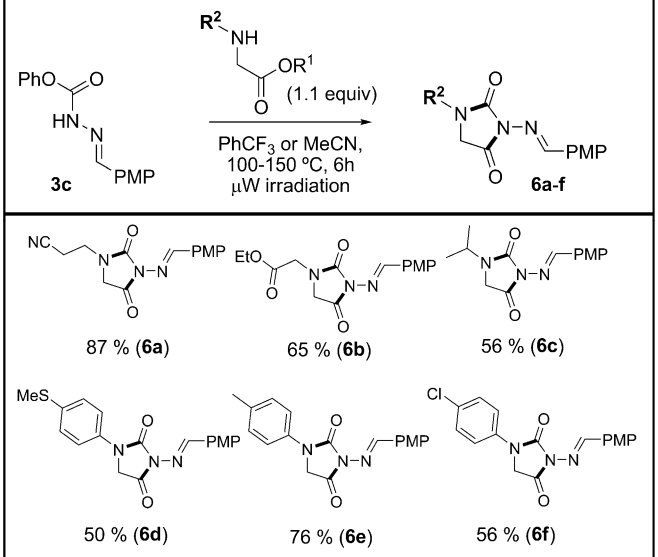


[a] Conditions: Carbazate (1 equiv), amino ester (1.1 equiv), *i*Pr$_2$NEt (1.2 equiv) in PhCF$_3$ (0.3 M), heated at 100 °C for 6 h (sealed vial, microwave reactor).

hyde- and ketone-derived hydrazones (**3a–f** vs. **3g–i**). We were pleased that electron-rich (**3c**,**f**) and electron-poor (**3d**,**e**) aromatic hydrazones proved applicable reagents. In general, higher yields were obtained using hydrazones (Table 2), rather than hydrazides (Table 1), as isocyanate precursors, which is in line with the easier purification of the products by chromatography.

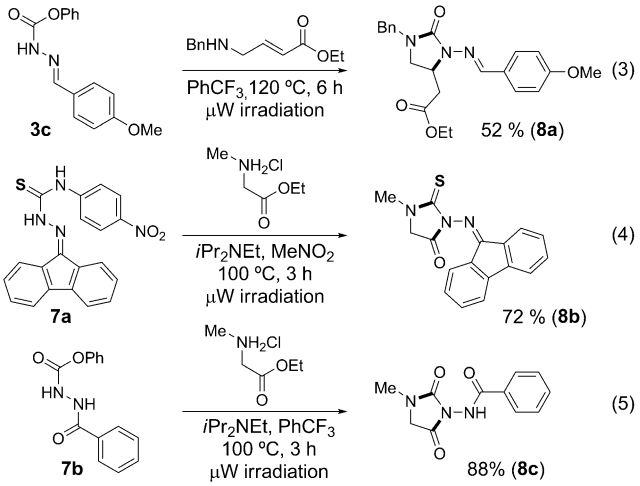
Pleased by the generality of the cascade with hydrazones, we proceeded to survey its applicability by treating several amino esters with anisole-derived hydrazone **3c** (Table 3). Gratifyingly, various functional groups were tolerated on the α-amino ester partner. For example, a nitrile did not interfere with the cyclization and yielded the hydantoin **6a** in excellent yield. Addition/cyclization using diethyl iminodiacetate also provided the ester-substituted hydantoin **6b**. More sterically hindered substituents on the nitrogen of the α-amino ester were also tolerated, as observed for the formation of *N*-isopropyl (**6c**) and *N*-aryl (**6d–f**) hydantoins. We were very pleased that *N*-aryl glycine esters proved competent reaction partners (**6d–f**), since anilines are rather poor nucleophiles. However, this result is in line with the proposed involvement of iminoisocyanate intermediates, given their high electrophilicity.[5]

Table 3. Cascade reaction of several α-amino esters with hydrazone **3c**.[a,b]



[a] Conditions: Carbazate (1 equiv), amino ester (1.1 equiv), iPr_2NEt (1.2 equiv) in $PhCF_3$ or MeCN (0.3 M), heated for 6 h (sealed vial, microwave reactor); [c] *T*: **6a**: 100 °C, **6b**: 120 °C, **6c–f**: 150 °C. PMP = *p*-methoxyphenyl.

At this stage we became interested in variations of this cascade to form other interesting classes of molecules. For example, we were pleased that a cascade involving substitution/cyclization via 1,4-addition occurred on a suitable amine precursor to yield imidazolidinone **8a** [Eq. (3)]. Next, we used a novel activated reagent to generate an amino-iso*thio*cyanate in situ and isolated amino*thio*hydantoin **8b** from a related cascade reaction [Eq. (4) vs. **4i** (Table 2)].[12] Moreover, we were also able to cyclize acyl carbazate **7b** to yield amidohydantoin **8c** [Eq. (5)]. Overall, these extensions further highlight that this substitution/cyclization sequence is broadly applicable for the synthesis of complex aminohydantoins and related heterocycles.

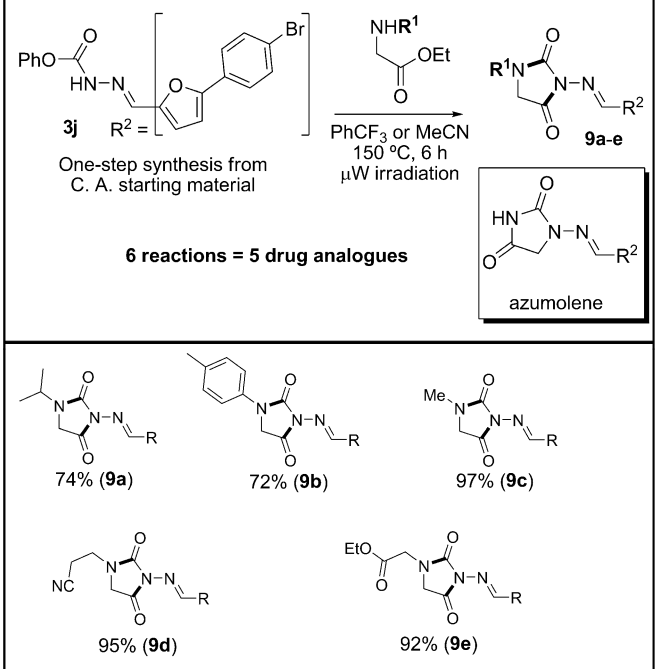


Finally, we looked at the potential of our method for medicinal chemistry purposes. As previously mentioned, aminohydantoin subunits are present in many pharmaceuticals; however, the hydantoin core often lacks substitution. We thus became interested in a late-stage formation of substituted hydantoins from a common precursor. Our approach led to the rapid formation of several products related to azumolene (Table 4), a veterinary drug that displays unique activity.[13]

As illustrated, a variety of *N*-substituted azumolene analogues were formed in good to excellent yields from a common hydrazone (**3j**; Table 4). Strategically, this late-stage hydantoin assembly nicely complements other approaches involving diversification from a common N–H aminohydantoin precursor. For example, *N*-alkylation can be challenging (e.g. secondary substituents, **3g**), and *N*-arylation can be problematic in the presence of aromatic halides (e.g. the bromide present in **3j**). Gratifyingly the assembly of both *N*-alkyl (**9b**,**d–f**) and *N*-aryl (**9c**) iminohydantoins was achieved in one step and was amenable to the incorporation of functional groups (**9d**,**e**). We were also pleased to see that no silica gel column was necessary for the purification of the intermediate or any of the final compounds, making this method practical for late-stage incorporation of an iminohydantoin subunit.

In summary, we have developed a cascade reaction forming aminohydantoins relying on the use of simple hydrazides and hydrazones as precursors of *N*-substituted isocyanates. The cascade relies on the addition of α-amino esters to isocyanate intermediates generated in situ, followed by cyclization to afford the desired hydantoins. The broad applicability of the reaction sequence is remarkable considering that *N*-substituted-isocyanates are amphoteric molecules, and that this amphotericity is known to lead to unwanted side reactions (e.g. dimerization).

Table 4. Cascade synthesis of azumolene analogues.[a]



[a] Conditions: Carbazate (1 equiv), amino ester (1.1 equiv), iPr$_2$NEt (1.2 equiv) in $PhCF_3$ or MeCN (0.3 M), heated at 150 °C for 6 h (sealed vial, microwave). C.A. = Commercially Available.

Overall, these results highlight the synthetic potential of these rarely utilized *N*-substituted-isocyanates in heterocycle synthesis and medicinal chemistry. The discovery of new reaction sequences building on this work is ongoing and will be reported in due course.

Experimental Section

An oven-dried microwave tube with a stir bar was capped with a septum, purged with argon, and fitted with an outlet for 5 min. The carbazate (1.0 equiv), amino ester hydrochloride salt (1.1 equiv), *N*,*N*-diisopropylethylamine (1.2 equiv) and α,α,α-trifluorotoluene (0.3 M) were added to the seal tube, while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a microwave cap and heated for six hours at 80–150 °C. The tube was allowed to cool to ambient temperature, concentrated under reduced pressure, and purified by silica gel chromatography to give the corresponding products. See the Supporting Information for details.

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Keywords: cascade reactions · hydantoins · isocyanates · isothiocyanates · synthetic methods

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COMMUNICATION

Cascade Reactions

*J.-F. Vincent-Rocan, C. Clavette, K. Leckett, A. M. Beauchemin**

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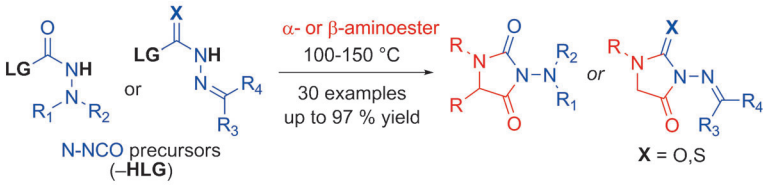
A Cascade Synthesis of Aminohydantoins Using In Situ-Generated *N*-Substituted Isocyanates



Go seek hydantoins: In contrast to normal (*C*-substituted) isocyanates, *N*-substituted isocyanates are rarely used in synthesis. However, simple hydrazides and hydrazones can act as bench-stable precursors, yet release the amphoteric isocyanates upon heating. A cascade reaction exploiting these intermediates rapidly assembles the medicinally important aminohydantoin motif.