Multicomponent Synthesis of *N*-Carbamoyl Hydantoin Derivatives

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Abstract: A novel, three-component process for the preparation of a small library of unprecedented nonracemic *N*-carbamoyl hydantoins under very mild conditions, as well as the hypothetic mechanism, are presented.

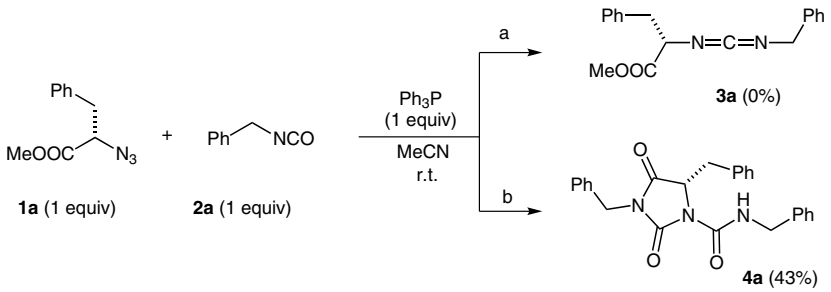
Key words: domino reaction, multicomponent reaction, heterocycles, hydantoins, Staudinger reaction

During the last years, multicomponent (MC) reactions have been often involved in combinatorial and diversity-oriented synthesis programs, becoming an extremely powerful tool in medicinal chemistry.[1] Indeed, MC reactions have different advantages compared to the traditional multistep reaction sequences, mainly considering the operational simplicity, bond-forming efficiency, highly flexibility, easily achievement of molecular complexity, and all the economical and environmental aspects associated with the minimization of waste production and manpower. Although MC processes have been applied with success to the synthesis of different kind of scaffolds, many of them have been developed for the efficient construction of even simple heterocycles.[2] For all these reasons, the design and the application of novel MC reactions for the construction of suitably functionalized heterocyclic scaffolds is a very active area of research both in academia and in industry. Among the various heterocycles, the hydantoin ring could be considered a 'privileged' scaffold since it has been widely used in numerous pharmaceutical applications.[3]

In this context, we have recently discovered a MC sequential domino process for the synthesis of differently substituted hydantoins under mild conditions starting from in situ prepared carbodiimides.[4] The same process has been further used for the preparation of glyco-hydantoin conjugates starting from carbodiimide bearing a sugar moiety.[5] Since it has been demonstrated that the hydantoin ring is able to induce conformational restriction in the backbone of peptidomimetics being, for instance, a suitable scaffold for the design of β-strand mimic structures,[6] we became interested in the preparation of hydantoin-based peptidomimetics starting from carbodiimides bearing an amino acid. Following our chemistry, such carbodiimides could have been prepared from Staudinger reaction between α-azido esters and isocyanates (Scheme 1, path a).

However, by reacting α-azido ester **1a** with one equivalent of benzyl isocyanate **2a** in acetonitrile at room temperature and in the presence of Ph_3P, we did not detect the formation of the expected carbodiimide **3a**, but we recovered a product that, after careful analysis, we hypothesized to be the *N*-carbamoyl hydantoin **4a** (Scheme 1, path b).[7] It is worth noting that hypothetic *N*-carbamoyl hydantoin **4a** contains two equivalents of benzyl isocyanate, thus the yields obtained carrying out the reaction with only one equivalent of isocyanate **2a** (43%) are very promising. In order to verify the structure assigned, we checked the literature and, to our big surprise, we did not find any example of nonracemic *N*-carbamoyl hydantoin derivative. Thus we decided to synthesize **4a** through the sequence depicted in Scheme 2.

Hydantoin **6** has been synthesized as described by Cuny et al., namely the preparation of phenylalanine benzyl amide by reaction of phenylalanine methyl ester **5** with benzyl amine, following by cyclization promoted by triphosgene.[8] Thus, carbamoylation of **6** has been obtained by de-



Scheme 1 Synthesis of *N*-carbamoyl hydantoin **3a**

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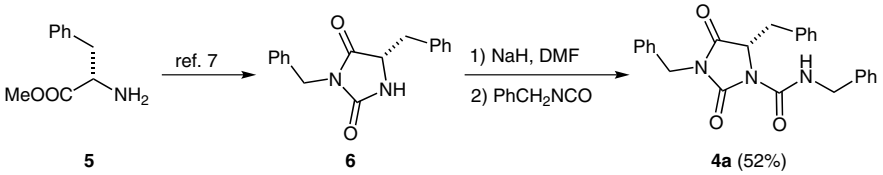


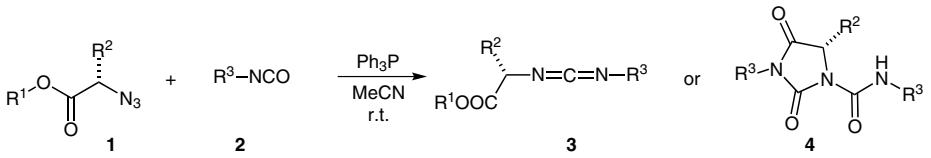
Scheme 2 Multistep synthesis of *N*-carbamoyl hydantoin **3a**

protonation with NaH followed by reaction with benzyl isocyanate, producing derivative **4a** in 52% yield. By comparing the ^{1}H NMR and ^{13}C NMR spectra of the two structures, we confirmed that the product obtained by our methodology was effectively the *N*-carbamoyl hydantoin **4a**. Unfortunately, the latter was found to have an enantiomeric excess of almost 60%, thus a partial epimerization occurred during our process.[9] However, it is worth noting that the synthetic plan depicted in Scheme 2 consists in a three-step sequence with the last step arising in moderate yields.

Thus our methodology looks particularly suitable and efficient for the preparation of such unprecedented compounds.

To determine the scope and limits of this methodology, we decided to study more in depth such MC processes starting from different α-azido esters **1** and isocyanates **2** (Table 1).[10,11]

Table 1 Synthesis of *N*-Carbamoyl Hydantoins



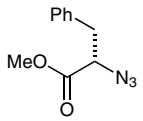
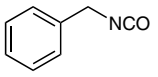
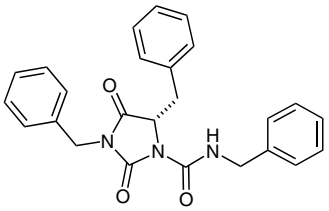
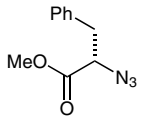
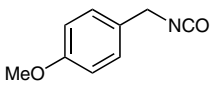
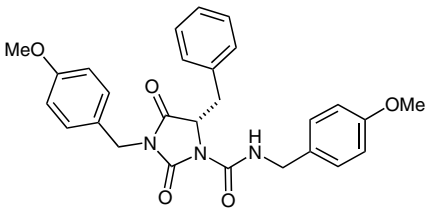
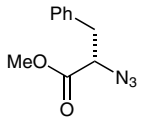
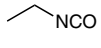
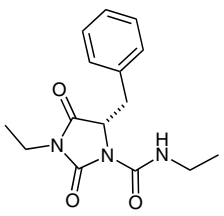
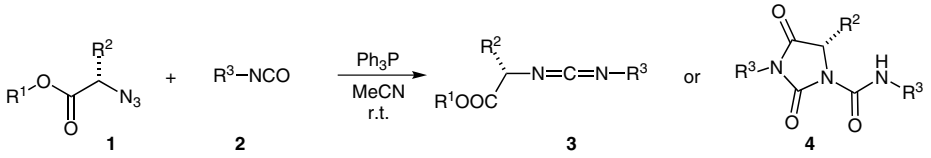
Entry	R^1	R^2	α-Azido esters	R^3	Isocyanate	Product	Yield (%)[a]
1	Me	Bn	 **1a**	Bn	 **2a**	 **4a**	90
2	Me	Bn	 **1a**	4-$MeOC_6H_4CH_2$	 **2b**	 **4b**	92
3	Me	Bn	 **1a**	Et	 **2c**	 **4c**	91

Table 1 Synthesis of *N*-Carbamoyl Hydantoins (continued)



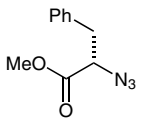
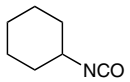
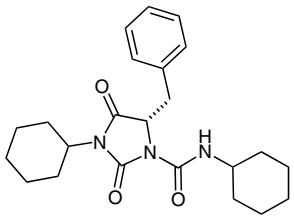
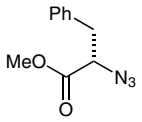
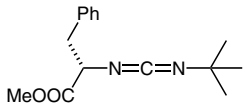
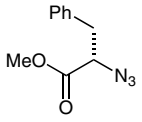
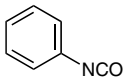
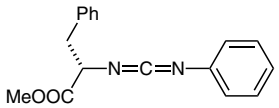
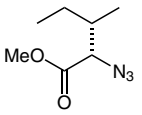
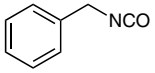
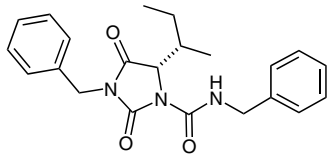
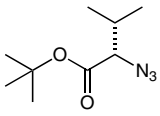
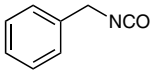
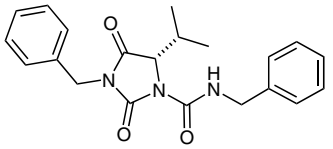
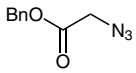
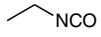
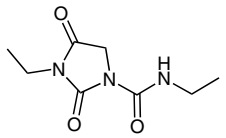
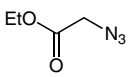
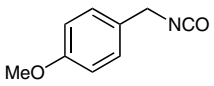
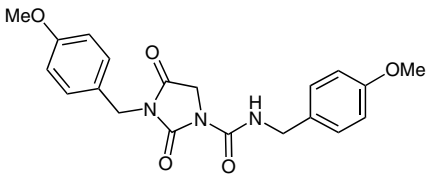
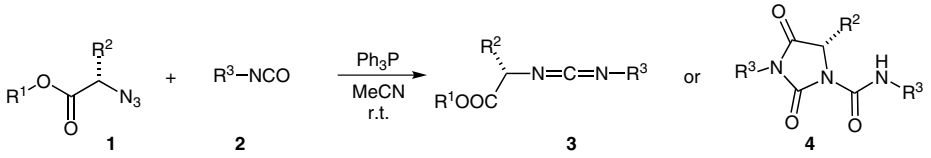
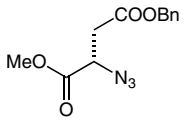
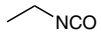
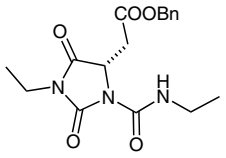
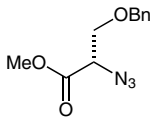
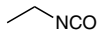
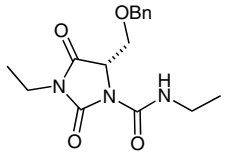
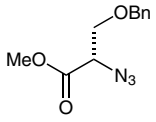
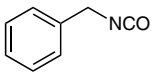
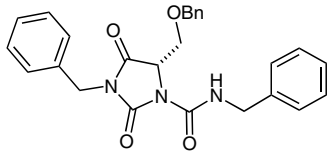
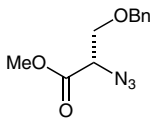
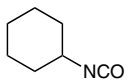
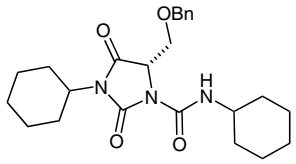
Entry	R^1	R^2	α-Azido esters	R^3	Isocyanate	Product	Yield (%)[a]
4	Me	Bn	 **1a**	*c*-Hex	 **2d**	 **4d**	76
5	Me	Bn	 **1a**	*t*-Bu	 **2e**	 **3a**	71
6	Me	Bn	 **1a**	Ph	 **2f**	 **3b**	73
7	Me	*s*-Bu	 **1b**	Bn	 **2a**	 **4e**	68[b]
8	*t*-Bu	*i*-Bu	 **1c**	Bn	 **2a**	 **4f**	21[c]
9	Bn	H	 **1d**	Et	 **2c**	 **4g**	89
10	Et	H	 **1e**	4-$MeOC_6H_4CH_2$	 **2b**	 **4h**	85

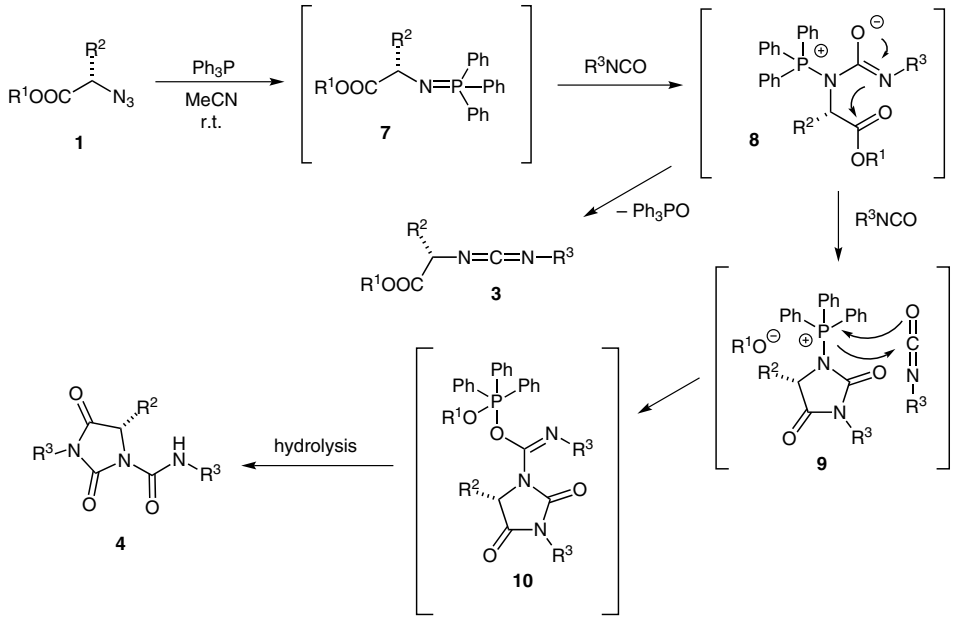
Table 1 Synthesis of *N*-Carbamoyl Hydantoins (continued)



Entry	R^1	R^2	α-Azido esters	R^3	Isocyanate	Product	Yield (%)[a]
11	Me	CH_2CO_2Bn	 **1f**	Et	 **2c**	 **4i**	68
12	Me	CH_2OBn	 **1g**	Et	 **2c**	 **4j**	76
13	Me	CH_2OBn	 **1g**	Bn	 **2a**	 **4k**	73
14	Me	CH_2OBn	 **1g**	*c*-Hex	 **2d**	 **4l**	70

[a] Isolated yields.
[b] The corresponding carbodiimide was isolated in10% yield.
[c] The corresponding carbodiimide was isolated in 64% yield.

First, we checked the efficiency of the process by increasing the amount of the isocyanate. Gratifyingly, by carrying out the reaction of α-azido ester **4a** with 2.5 equivalents of **2a** under the same conditions described above, namely room temperature and MeCN as solvent, we obtained the formation of hydantoin **4a** in almost quantitative yields (Table 1, entry 1). The process worked very efficiently with either primary and secondary alkyl isocyanates. Indeed, the same α-azido ester **4a** reacted smoothly with 4-methoxybenzyl (**2b**), ethyl (**2c**), and cyclohexyl isocyanate (**2d**) giving rise to the formation of the corresponding *N*-carbamoyl hydantoin **4b**–**d**, respectively, in excellent yields (Table 1, entries 2–4). Unfortunately, the reaction with tertiary alkyl isocyanates, such as *tert*-butyl isocyanate (**2e**), did not afford the expected hydantoin derivative, but the corresponding carbodiimide **3a** in good yields (Table 1, entry 5). The same result, namely the production of the carbodiimide **3b** instead of the hydantoin derivative, was obtained performing the reaction with aromatic isocyanates (Table 1, entry 6). Probably, the nucleophilic character of the amino moiety on the isocyanate reactant plays an important role on the outcome of the process and neither bulky *tert*-butyl nor electron-withdrawing phenyl substituents are suitable to trigger the mechanism which promotes the formation of the *N*-carbamoyl hydantoin. On the contrary, the steric hindrance of the α-azido ester side chain has minor influence on the yields of the process. Indeed, azido isoleucine methyl ester (**1b**) reacted with benzyl isocyanate (**2a**) producing the expected hydantoin derivative **4e** in good yields (Table 1, entry 7). As expected, since one step of the process is clearly a nucleophilic attack to the ester moiety of the starting azide, the reaction between α-azidovaline *tert*-butyl ester (**1c**) and benzyl isocyanate (**2a**) lead to the formation of hydantoin **4f** in low yields (Table 1, entry 8). On the contrary, either α-azidoglycine benzyl ester (**1d**) and



Scheme 3 Proposed mechanism for the MC synthesis of *N*-carbamoyl hydantoin **3**

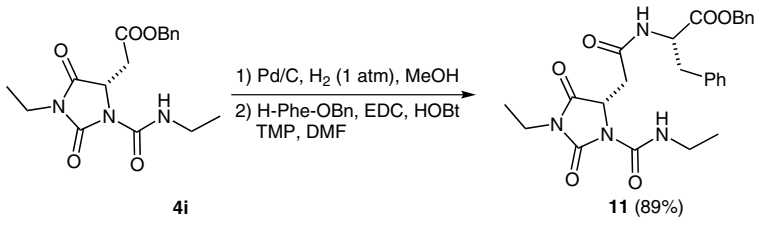
ethyl ester (**1e**) reacted straightforwardly with ethyl isocyanate (**2c**) and 4-methoxybenzyl isocyanate (**2b**) producing *N*-carbamoyl hydantoins **4g**,**h**, respectively, in very good yields (Table 1, entries 9 and 10). Finally, we explored the reaction with other starting α-azido esters, such as α-azido aspartic acid derivative **1f** and α-azido serine derivative **1g** with good results. Indeed **1f** reacted with ethyl isocyanate (**2c**) producing hydantoin derivative **4i** in satisfactory yields (Table 1, entry 11), while **1g** was treated with isocyanates **2a**,**c**,**d** giving rise to the efficient formation of products **4j–l**, respectively (Table 1, entries 12–14).

In agreement with all the experimental results described above, we suggest that our process proceeds through the mechanism portrayed in Scheme 3.

Phosphazene **7**, obtained by reaction between α-azido ester **1** and Ph_3P, reacts with the first equivalent of isocyanate **2** leading to the formation of zwitterionic intermediate **8**, which likely undergoes cyclization producing the heterocyclic intermediate **9**. When such cyclization is hampered by steric factors, mainly due to the isocyanate and the ester substituents rather than the R^2 group, the intermediate **8** can rearrange through the classical mechanism of the Staudinger reaction producing carbodiimide **3** as the main, if not the sole reaction product. The same behavior, namely the formation of the carbodiimide, was observed when the amino moiety of the isocyanate was poorly nucleophilic such as in phenylisocyanate. However, when heterocycle **9** is formed, it reacts with a second equivalent of isocyanate **2** leading to the formation of intermediate **10** which readily hydrolyzes to the final *N*-carbamoyl hydantoin **4**.

In order to prove the enantiomeric excesses of the *N*-carbamoyl hydantoins obtained and that some of them could be selectively functionalized, the ester moiety of compound **4i** was hydrolyzed by catalytic hydrogenation and the resulting acid coupled with (*S*)-H-Phe-OBn achieving the formation of **11** in very good overall yields as an almost 80:20 mixture (60% ee of the starting hydantoin) of diastereoisomers (Scheme 4).[12]

In conclusion, starting from easily accessible α-azido esters and isocyanates, we have developed a novel three-component process for the synthesis of unprecedented nonracemic *N*-carbamoyl hydantoins incorporating two equivalents of the isocyanate. When the reaction is not hampered by steric factors or poor nucleophilicity of the isocyanate amino moiety, the process works very well, producing the target compounds in high yields and under very mild conditions, that is, room temperature without the need of bases or acids. The synthesis of *N*-carbamoyl



Scheme 4 Synthesis of **11**

hydantoins incorporating two different isocyanates, the reactivity of carbodiimides **3**, as well as the application of the process for the solid-phase and combinatorial synthesis of libraries of *N*-carbamoyl hydantoins is currently in progress in our laboratories.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(7) **Characterization of Compound 4a**
R_f = 0.43 (hexane–EtOAc, 60:40); $[a]_D^{20}$ +33.3 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.17 (t, *J* = 5.6 Hz, 1 H), 7.38–6.97 (m, 15 H), 4.83 (dd, *J* = 5.6, 2.4 Hz, 1 H), 4.62 (dd, *J* = 14.8, 6.0 Hz, 1 H), 4.52 (d, *J* = 14.8 Hz, 1 H), 4.50 (dd, *J* = 14.8, 6.8 Hz, 1 H), 3.70 (dd, *J* = 14.0, 5.6 Hz, 1 H), 3.30 (dd, *J* = 14.0, 2.4 Hz, 1 H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 170.5, 155.3, 151.1, 138.0, 133.3, 129.7, 128.7, 128.6, 128.5, 128.2, 128.0, 127.6, 127.4, 59.9, 43.9, 42.4, 34.9. ESI-MS: *m/z* (%) = 259.1 (100), 436.2 (38) $[M^+ + H]$. Anal. Calcd for $C_{25}H_{23}N_3O_3$: C, 72.62, H, 5.61, N, 10.16. Found: C, 72.67, H, 5.64, N, 10.11.

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(9) The ee was determined by chiral HPLC (see Supporting Information). In this regard, we would like to acknowledge the referee who suggested we check the ee of the *N*-carbamoyl hydantoins obtained by our process.

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(11) **General Procedure for the Preparation of *N*-Carbamoyl Hydantoins 4**
To a stirred solution of α-azido ester **1** (1equiv) and isocyanate **2** (2.5 equiv) in MeCN (0.1 M solution), solid Ph_3P (1equiv) was added and the solution stirred at r.t. for 3 h. The solvent was removed under reduced pressure and the crude purified by flash chromatography.

(12) Since both *N*-carbamoyl hydantoins **4a** and **4i** have ca. 60% ee, we assume that also *N*-carbamoyl hydantoins **4b–f,k–l** posses the same ee since the process was run under the same conditions, i.e., in MeCN at r.t. for 3 h.

