

One-Pot, Regioselective Synthesis of 1,3,5 Trisubstituted Hydantoin s by Domino Condensation/aza-Michael/O→N acyl Migration of Asymmetric Carbodiimides with α,β -Unsaturated Carboxylic Acids

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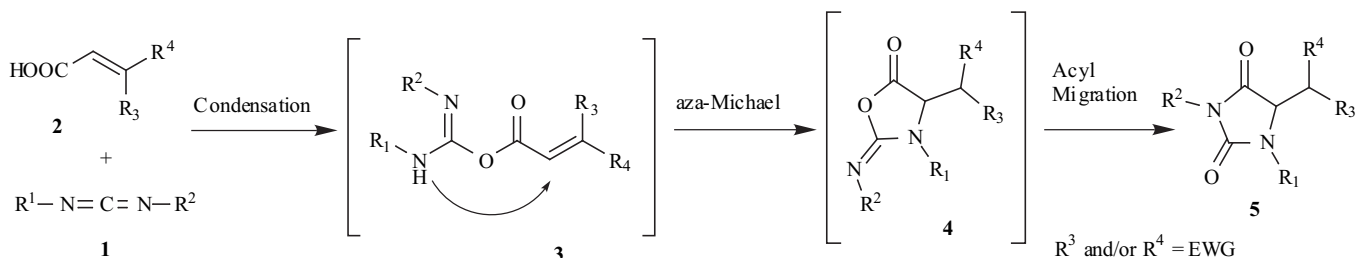
Received June 29, 2004; Accepted July 29, 2004

Abstract—1,3,5 Trisubstituted hydantoin s having two different substituents at the nitrogen atoms could be smoothly prepared by a domino condensation/aza-Michael/O→N acyl migration of asymmetric carbodiimides with activated α,β -unsaturated carboxylic acids. The regiochemical outcome of the process, as well as scope and limits, are discussed.

Keywords: Hydantoin s, domino reaction, aza-Michael, carbodiimides, regiochemistry.

Hydantoin s have been widely used in biological screenings resulting in numerous pharmaceutical applications [1]. The observed activity usually does not arise from the heterocycle itself but from different ligands that have been attached to it. For this reason there is a lot of interest in developing new strategies for a straightforward synthesis of structurally diverse, highly substituted hydantoin s both in

carbodiimides ($R^1 \neq R^2$), that dramatically expands the scope of the process and allows for the preparation of a potentially very large array of structurally diverse hydantoin s. We show herein that a judicious choice of substituents on the carbodiimide framework leads to an efficient and regioselective reaction, that produces 1,3,5 trisubstituted hydantoin s **5** bearing different R^1 and R^2



Scheme 1. The one-pot domino condensation/aza-Michael addition/ O→N acyl migration.

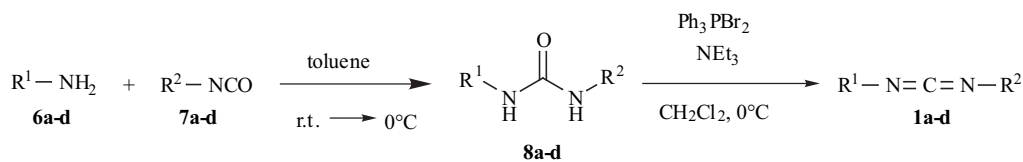
solution and in solid phase. Very recently, we have developed a new straightforward method for the synthesis of 1,3,5 trisubstituted hydantoin s **5** (Scheme 1) by a domino [2] condensation/aza-Michael addition/ O→N acyl migration of commercially available symmetric ($R^1 = R^2$) carbodiimides **1** (Scheme 1) with activated α,β unsaturated carboxylic acids **2** ($R^3 = H, CF_3, CO_2Et$; $R^4 = CO_2Et$), which proceeds under very mild conditions, possibly through the putative 2-imino-oxazolidin-5-one intermediate **4** [3]. In this communication we describe the outcome of the process starting from *ad-hoc* synthesized asymmetric

substituents at the two nitrogen atoms, and thus suitable for further selective modifications.

In order to investigate the possibility to achieve good regioselectivities through the key intramolecular aza-Michael step, we chose four asymmetric carbodiimides **1a-d** (Scheme 2 and Table 1) having different functionalities at nitrogen atoms in terms of nucleophilic character and/or steric bulkiness, depending on the R^1 and R^2 appendages [4]. Asymmetric carbodiimides **1a-d** were prepared by dehydration, with freshly prepared dibromotriphenylphosphorane [5] of the corresponding ureas **8a-d** obtained by reaction of amines **6a-d** with isocyanates **7a-d**.

First of all we investigated the reaction of activated α,β unsaturated carboxylic acids **2a-c** (Scheme 3) with highly reactive dialkyl carbodiimide **1a** bearing a primary alkyl group as a substituent of one nitrogen and a more congested *tert*-butyl substituent at the other nitrogen (Table 1, entries

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**Scheme 2.** Synthesis of asymmetric carbodiimides **1a-d**.**Table 1.** Synthesis of Asymmetric Carbodiimides **1**

Entry	Amine	Isocyanate	R ¹	R ²	Product (Yield %)	Product (Yield %)
1	6a	7a	Bn	<i>tert</i> Bu	8a (n.p.) ^a	1a (62)
2	6b	7b	4-CH ₃ O-C ₆ H ₄	Bn	8b (n.p.) ^a	1b (60)
3	6c	7c	Ph	<i>cyclo</i> Hexyl	8c (n.p.) ^a	1c (66)
4	6d	7d	4-NO ₂ -C ₆ H ₄	4-CH ₃ O-C ₆ H ₄	8d (60)	1d (51)

^a n.p. = Not purified.

1-3). The reaction is totally regioselective with the acids **2a,b** under the classical conditions in the absence of a base [3] (entries 1 and 2), and also with 4,4,4-trifluoro-3-trifluoromethyl-crotonic acid **2c** (entry 3), that required the use of an amine base [6], giving rise in good yields to the formation of the preferred hydantoins **13a-c** stemming from the nucleophilic attack of the less hindered benzyl amine moiety during the aza-Michael step.

Then, we investigated the reactivity of *N,N*-alkyl,aryl-carbodiimides **1b,c** derived from an amine bearing a primary or a secondary alkyl group (R¹), respectively, and an aryl (R²) amine (Table 2, entries 4-8). Also in these cases, we exclusively obtained the formation of the products **13d-h** arising from the attack of the more nucleophilic nitrogen (bearing the alkyl substituent) of the initial adduct **9** (Scheme 3) during the aza-Michael step leading to the intermediate **11**. Mixed *N,N*-alkyl,aryl-carbodiimides **1b,c** were less reactive than dialkyl carbodiimide **1a** therefore good yields were achieved only with more activated acids **2a,c** (entries 5,6,8), while **2b** reacted affording moderate to low yields (entries 4,7) [7].

Finally, we tested the reactivity of carbodiimide **1d** having two different aromatic substituents (Table 2, entries

9-11). The regioselectivity in this case could arise from the higher electron density, and therefore higher nucleophilicity, on the nitrogen atom of the anisidine moiety (R¹) in **9** with respect to the electron-poor 4-nitro-aniline moiety (R²) in **10** (Scheme 3). However, the difference in reactivity of the two amine moieties turned out to be smaller than expected, and the resulting regioselectivity was lower than that observed in the previous cases. In fact, in the case of *N,N*-diaryl-carbodiimide **1d** moderate selectivity was achieved only with highly activated α,β carboxylic acids, such as **2a,c** (Table 2, entries 9,11), while no selectivity was observed with the less activated acid **2b** (entry 10).

In summary, we have performed the synthesis of an array of structurally diverse hydantoins **13a-m**, including fluorinated ones, having different substituents on the nitrogen atoms, thus suitable for further selective modifications. The new methodology is based on a domino reaction involving activated carboxylic acids **2a-c** and asymmetric carbodiimides **1a-d**. The regioselectivity of the process depends, firstly, on the different nucleophilic character and/or bulkiness on the carbodiimide nitrogen atoms and, secondly, on the reactivity of the α,β -unsaturated acids. Extension of the reaction to other activated α,β -unsaturated carboxylic acids as well as the application of the

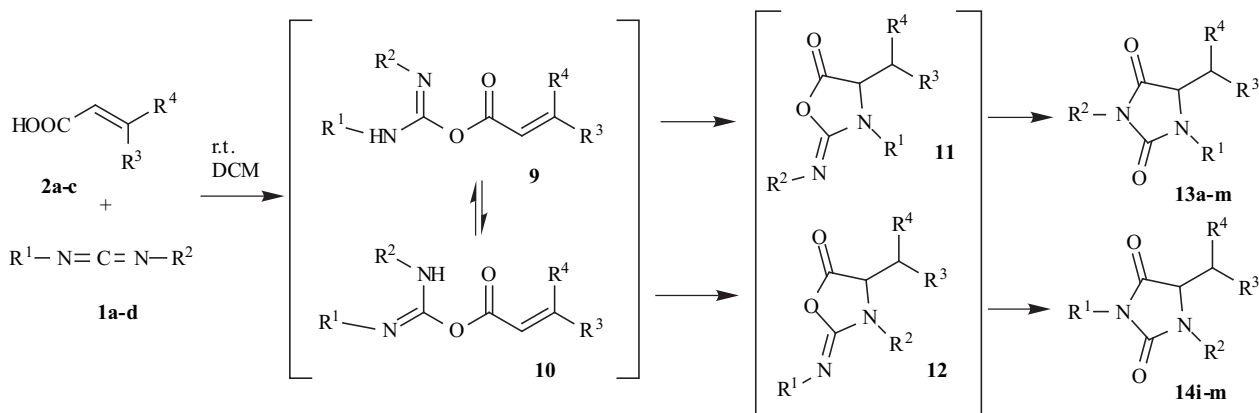
**Scheme 3.** The domino reaction of activated α,β -unsaturated acids **2** with asymmetric carbodiimides **1**.

Table 2. Synthesis of Structurally Modified Hydantoins 13,14

Entry	Carbodiimide	Acid	R ¹	R ²	R ³	R ⁴	Products	13/14	Yields (%)
1	1a	2a	Bn	<i>t</i> -Bu	CO ₂ Et	CO ₂ Et	13a	100/0	65
2	1a	2b	Bn	<i>t</i> -Bu	H	CO ₂ Et	13b	100/0	63 ^a
3	1a	2c	Bn	<i>t</i> -Bu	CF ₃	CF ₃	13c	100/0	75 ^{a,b}
4	1b	2b	Bn	PMP	H	CO ₂ Et	13d	100/0	47 ^a
5	1b	2c	Bn	PMP	CF ₃	CF ₃	13e	100/0	67 ^{a,b}
6	1c	2a	<i>c</i> -hex	Ph	CO ₂ Et	CO ₂ Et	13f	100/0	72
7	1c	2b	<i>c</i> -hex	Ph	H	CO ₂ Et	13g	100/0	29 ^a
8	1c	2c	<i>c</i> -hex	Ph	CF ₃	CF ₃	13h	100/0	83 ^{a,b}
9	1d	2a	PMP	4-NO ₂ -C ₆ H ₄	CO ₂ Et	CO ₂ Et	13, 14i	75/25	65
10	1d	2b	PMP	4-NO ₂ -C ₆ H ₄	H	CO ₂ Et	13, 14l	50/50	63 ^a
11	1d	2c	PMP	4-NO ₂ -C ₆ H ₄	CF ₃	CF ₃	13, 14m	80/20	75 ^{a,b}

^aOvernight. Otherwise the reaction time was 5 minutes.

^bAn equiv. of a base (*sym*-collidine) was used.

process to the solid-phase/combinatorial synthesis are currently being investigated.

EXPERIMENTAL

General Procedure for the Synthesis of Asymmetric Carbodiimides 1a-c

To a stirred 1 M solution of isocyanate **7** (1 equiv.) in toluene a 1 M solution of the amine **6** (1 equiv.) in toluene was added dropwise at room temperature. Then, the resulting suspension was cooled at 0 °C, maintained at that temperature for 30 min and filtered. The obtained solid (crude urea **8**) was added portionwise during 1 hour to a freshly prepared 0.5 M suspension of Ph₃PBr₂ (1.25 equiv.) and dry TEA (2.5 equiv.) in dry DCM at 0 °C. The resulting suspension was kept at room temperature and washed with water. The organic phase was dried with Na₂SO₄, filtered and the solvent removed in vacuo. The resulting solid was triturated in hexane, filtered and the hexane solution was concentrated under reduced pressure giving the carbodiimides **1** that were used without any further purification for the next step.

General Procedure for the Synthesis of Hydantoins 13,14

To a stirred solution of α,β -unsaturated acid **2** (1 mmol) in DCM (3 ml), crude carbodiimide **1** (1 mmol) (see above) was added. After consumption of the starting material (TLC) the organic solvent was evaporated and the crude purified by

flash chromatography on silica gel, affording pure hydantoins **13** and **14**.

ACKNOWLEDGEMENTS

Politecnico di Milano and CNR are gratefully acknowledged for economic support.

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- [6] Reactions of **2c** carried out in absence of a base produced the corresponding hydantoin in only modest yields.
- [7] In the case of entries 4,7 the O→N acyl migration of *O*-acylisoureas **9** (Scheme 3) was competitive with the intramolecular aza-Michael step, leading to the formation of the corresponding *N*-acyl ureas as major products. The latter compounds are stable and did not convert spontaneously into hydantoins at r.t.. For a detailed study and discussion of the mechanism of the title reaction see Ref. 3a, as well as: Kishikawa, K.; Sankhavasi, W.; Yoshizaki, K.; Kohmoto, S.; Yamamoto, M.; Yamada, K. *J. Chem. Soc. Perkin Trans. 1* **1994**, 1205-1209.