Pergamon

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Tetrahedron Letters 44 (2003) 8549–8551

TETRAHEDRON LETTERS

Domino condensation/aza-Michael/O→N acyl migration of carbodiimides with activated α,β-unsaturated carboxylic acids to form hydantoins

Alessandro Volonterio[a,*] and Matteo Zanda[b,*]

[a]*Dipartimento di Chimica, Materiali ed Ingegneria Chimica 'G. Natta' del Politecnico di Milano, via Mancinelli 7, I-20131 Milano, Italy*

[b]*C.N.R., Istituto di Chimica del Riconoscimento Molecolare, sezione 'A. Quilico', via Mancinelli 7, I-20131 Milano, Italy*

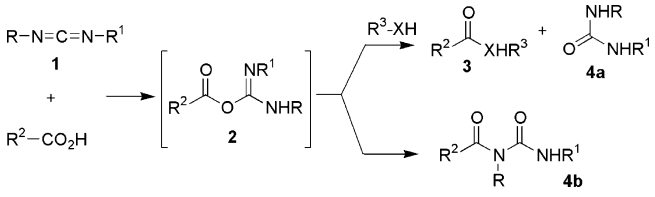
Received 16 July 2003; revised 4 September 2003; accepted 17 September 2003

Abstract—Activated α,β-unsaturated carboxylic acids undergo an unexpected domino condensation/aza-Michael/O→N acyl migration with carbodiimides, producing *N*,*N*-disubstituted hydantoins in good yields. An array of structurally varied aspartic acid-derived hydantoins, including some fluorinated derivatives, have been synthesized by this method, whose scope and limits are discussed.

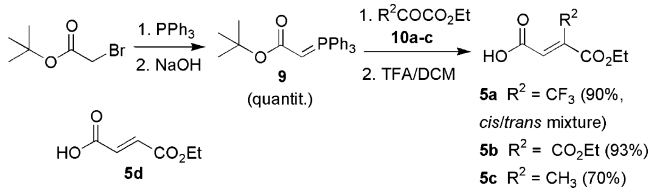
Hydantoins are an important class of bio-active molecules.[1] New efficient methods for the rapid generation of structurally varied and functionalized hydantoins are strongly desirable. In this communication we describe a new domino[2] condensation/aza-Michael addition/O→N acyl migration of carbodiimides with fumaric and maleic acid derivatives. The reaction smoothly produces aspartic acid-derived hydantoins otherwise difficult to obtain, including some fluorinated derivatives which can serve as precursors of the corresponding amino acids.[3]

Carbodiimides **1** (Scheme 1), such as DCC,[4] DIC and EDC are popular condensing agents extensively used to promote the coupling reaction of carboxylic acids with alcohols, amines and amino acids (R^3-XH) affording, respectively, esters, amides and peptides **3**, together with a urea coproduct **4a**, through an intermediate *O*-acylisourea **2**. In the absence of R^3-XH, **2** rearranges spontaneously via O→N acyl migration to the *N*-acylurea **4b**, which is a frequently found byproduct in these reactions.[5] Carbodiimide-promoted couplings with α,β-unsaturated carboxylic acids are known to produce large amounts of byproducts **4b**.[6]

The starting α,β-unsaturated carboxylic acids **5a–c** (Scheme 2) were prepared by Wittig reaction of the stabilized ylide **9** with the ketones **10a–c**, whereas fumaric acid monoethyl ester **5d** is commercially available. Interestingly, **5c** ($R^2=CH_3$) was obtained in geometrically homogeneous *E*-form, while **5a** ($R^2=CF_3$) was obtained as a nearly equimolar *Z*/*E* mixture.



Scheme 1. Carbodiimide-promoted coupling of carboxylic acids.



Scheme 2. Preparation of the starting α,β-unsaturated carboxylic acids **5**.

Keywords: hydantoins; domino reaction; aza-Michael; carbodiimides.

* Corresponding authors. E-mail: alessandro.volonterio@polimi.it; matteo.zanda@polimi.it

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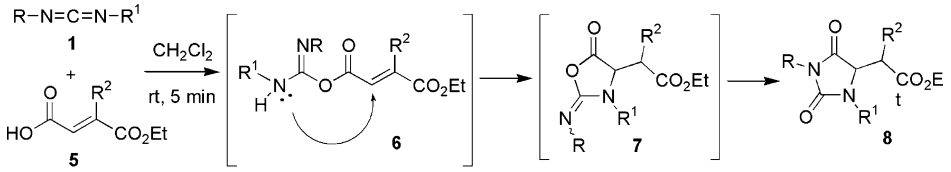
doi:10.1016/j.tetlet.2003.09.134



Scheme 3. The novel domino reaction.

Table 1. Scope of the novel domino reaction

Entry	Acid	Carbodiimide	R	R^1	R^2	Product	Yield (%)
1[a]	**5a**	**1a**	*cyclo*-Hexyl	*cyclo*-Hexyl	CF_3	**8a**	88[c]
2[a]	**5a**	**1b**	*iso*-Propyl	*iso*-Propyl	CF_3	**8b**	70[c]
3	*Z*-**5a**	**1b**	*iso*-Propyl	*iso*-Propyl	CF_3	**8b**	80[d]
4[a]	**5a**	**1c**	*n*-Propyl	$-(CH_2)_3NMe_2$	CF_3	**8c**	76[e]
5[a]	**5a**	**1d**	*tert*-Butyl	*tert*-Butyl	CF_3	**8d**	75[c]
6[a]	**5a**	**1e**	*p*-Tolyl	*p*-Tolyl	CF_3	**8e**	38[b,c]
7	**5b**	**1a**	*cyclo*-Hexyl	*cyclo*-Hexyl	CO_2Et	**8f**	60
8	**5b**	**1b**	*iso*-Propyl	*iso*-Propyl	CO_2Et	**8g**	70
9	**5b**	**1c**	*n*-Propyl	$-(CH_2)_3NMe_2$	CO_2Et	**8h**	70[h]
10	**5b**	**1d**	*tert*-Butyl	*tert*-Butyl	CO_2Et	**8i**	64
11	**5b**	**1e**	*p*-Tolyl	*p*-Tolyl	CO_2Et	**8j**	n.r.[f]
12	**5c**	**1d**	*tert*-Butyl	*tert*-Butyl	CH_3	**11c**[g]	40
13	**5d**	**1a**	*cyclo*-Hexyl	*cyclo*-Hexyl	H	**8k**	65[b]
14	**5d**	**1b**	*iso*-Propyl	*iso*-Propyl	H	**8l**	67[b]
15	**5d**	**1d**	*tert*-Butyl	*tert*-Butyl	H	**8m**	10[b]
16	**5d**	**1e**	*p*-Tolyl	*p*-Tolyl	H	**8n**	60[b]

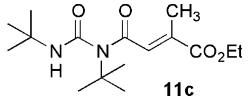
[a] **5a** used in nearly equimolar *E*/*Z* ratio.
[b] Overnight.
[c] Equimolar mixture of two diastereomers.
[d] Two diastereomers with d.r. = 2.5/1.0.
[e] Nearly equimolar mixture of four isomers.
[f] No reaction observed.
[g] The corresponding hydantoin did not form.
[h] Nearly equimolar mixture of two isomers.

Surprisingly, when carbodiimides **1** were reacted with the α,β-unsaturated acids **5** (Scheme 3), instead of the expected coupling products **3**, *N*,*N*-disubstituted hydantoins **8** were cleanly formed, generally in good yields (Table 1).[7] This process is likely to take place through the putative 2-imino-oxazolidin-5-one intermediate **7**,[8] which in turn is formed by intramolecular aza-Michael addition of the unsaturated *O*-acylisourea **6**.

Strongly activated acids **5a** (entries 1–6) and **5b** (entries 7–11) reacted smoothly (5 min) with *N*-dialkyl carbodiimides **1a**–**d** in CH_2Cl_2 at rt. Remarkably, even sterically hindered *tert*-butyl carbodiimide **1d** gave satisfactory results, affording **8d** and **8i** in good yields (entries 5 and 10, respectively).

p-Tolyl carbodiimide **1e** did not provide satisfactory results (entries 6 and 11), owing to the formation of an intermediate *O*-acylisourea **6** with poorly nucleophilic nitrogen atoms, and therefore scarcely reactive in the aza-Michael step. Less activated fumaric acid monoethyl ester **5d** required longer reaction times (CH_2Cl_2, overnight, rt) but satisfactory results were obtained as well with **1a**, **1b** and even **1e**, while **1d** reacted sluggishly (entries 13–16).[9] These results suggest that the loss of electrophilicity in **5d** is counterbalanced by a diminished steric hindrance at C-3. 3,3-Disubstituted acid **5c** was found to be reactive toward **1d** only in the condensation step (entry 12) affording the rearranged *N*-acylurea product **11c** (Fig. 1) in modest yields, as a likely result of severe steric hindrance at C-3 which hampers the intramolecular aza-Michael step.

Concerning the stereochemical aspect, one can notice that the β-trifluoromethyl-fumarate **5a** gives rise to hydantoins **8a**–**e** which exist in two diastereomeric forms. However, under the experimental conditions explored so far, the process is scarcely stereoselective. In fact, a low d.r. was obtained not only from the *E*/*Z* mixture of acid **5a** (entries 1–5), but even from homogeneously *Z*-configured **5a** (entry 6).[10] Concerning the reactions with **1c** (EDC), hydantoins **8c**,**h** (entries 4 and 9) formed as mixtures of two isomers originating from the poorly chemoselective aza-Michael attack of either the NH-*n*Pr (R) or the NH-$(CH_2)_3NMe_2$ (R^1) groups.



11c

Figure 1. *N*-Acylurea byproduct obtained from **5c**.

The structures of some of the hydantoin products, such as **8k** and **8l**, were confirmed by correlation with the compounds described in the literature.[7]

In order to gain a deeper insight into the mechanism of this domino process, the reaction between **1d** and **5b** (see Table 1, entry 10) was performed in an NMR tube. Unfortunately, neither ^{1}H nor ^{13}C NMR spectroscopy allowed us to detect any putative intermediate such as **6** or **7** (Scheme 3), since the final hydantoin **8i** formed very rapidly.

In summary, we have described a new domino reaction effectively producing aspartic-acid derived hydantoins **8** from carbodiimides **1** and activated α,β-unsaturated acids **5**. The process is operationally very simple, fast, employs easily available reagents and can be used to produce arrays of structurally diverse hydantoins, including fluorinated ones. Extension of the reaction to other activated α,β-unsaturated carboxylic acids, and a stereoselective version of the process are currently being investigated.

Acknowledgements

We thank MIUR (Cofin 2002, Project 'Peptidi Sintetici Bioattivi'), Politecnico di Milano and C.N.R. for economic support.

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7. A conceptually related process involving fumaric acid monomethyl ester and several carbodiimides, in the presence of alcohols and amines, was reported to produce rearranged urea products via the intermediates **6** and **7**. In that case, the corresponding hydantoins were occasionally observed as minor byproducts. See: Kishikawa, K.; Sankhavasi, W.; Yoshizaki, K.; Kohmoto, S.; Yamamoto, M.; Yamada, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1205–1209. No attempts to produce hydantoins and no description of the reaction course in the absence of alcohols or amines were described therein.
8. 2-Imino-oxazolidin-5-ones **7** have been described and isolated: Brady, W. T.; Owens, R. A. *J. Org. Chem.* **1977**, *42*, 3220–3222.
9. The use of a catalytic base (DMAP or *sym*-collidine) did not improve the outcome of the reactions involving **5d**.
10. A sample of diastereomerically pure *Z*-**5a** was obtained by flash chromatography (*n*-Hex/EtOAc 8:2) of the mixture.