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A Mild, Efficient Approach for the Synthesis of 1,5-Disubstituted Hydantoins

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An efficient and straightforward two-step procedure for the synthesis of *N*-1 alkyl/aryl-substituted hydantoins was developed, starting from easily available starting materials. The procedure envisages a highly regiospecific domino condensation/aza-Michael (nucleophilic substitution)/O→N acyl migration between activated α,β-unsaturated carboxylic acids or α-haloaryl acetic acids, respectively, and *N*-*tert*-butyl- or *N*-tritylcarbodiimides, leading to the regioselective formation of hydantoins bearing the tertiary alkylic substituent in the 3-position, followed by selective removal the substituent. This process avoids the use of harsh reaction conditions and toxic reagents and is high yielding. A detailed study of the influence of the structure of the reactants on the reaction outcome is presented. A wide variety of final products having a primary, secondary, cyclic and aryl substituent at the N-1 position were successfully synthesized by this method.

Introduction

Hydantoins have been widely used in biological screenings resulting in numerous pharmaceutical applications. In fact, many derivatives have been identified as anticonvulsants[1] and antimuscarinics,[2] antiulcers and antiarrythmics,[3] antivirals, antidiabetics,[4] serotonin and fibrinogen receptor antagonists,[5] inhibitors of the glycine binding site of the NMDA receptor[6] and antagonists of leukocyte cell adhesion acting as allosteric inhibitors of the protein–protein interaction.[7] The observed activities usually do not arise from the heterocycle itself but from the different ligands that have been attached to it. Moreover, substituted hydantoins are important building blocks for the synthesis of nonnatural amino acids both in racemic form by alkaline degradation[8] and in an enantioselective way by enzymatic resolution.[9] For this reason, there is a lot of interest in developing new strategies for a straightforward synthesis of selectively substituted hydantoins both in solution and in the solid phase. To date, the most utilized strategy to prepare substituted hydantoins is the strongly acidic or basic cyclization of ureido acids obtained from reactions of amino acids or amino nitriles with alkyl, aryl or chlorosulfonyl isocyanates, respectively, which requires extended reaction times or high temperatures.[10] In this way, 3,5-di- and 3,5,5-trisubstituted hydantoins are readily accessible, whereas for the synthesis of 1,3,5-tri- and 1,3,5,5-tetrasubstituted hydantoins, it is necessary to perform a preliminary alkylation of the amino function by reductive amination[11] or by a Mitsunobu reaction.[12] Various different routes/methods for the synthesis of hydantoins have been recently developed both in solution and in the solid phase to improve the drawbacks associated with the above strategy.[11–13] In this context, we recently demonstrated that carbodiimides **2** when treated with suitable carboxylic acids **1**, namely, activated α,β-unsaturated acids and α-haloarylacetic acids, in the absence of a nucleophile are useful reagents for the straightforward synthesis of 1,3,5-trisubstituted hydantoins **3** through a regiospecific domino process consisting of a condensation step between the two reactants, leading to the formation of *O*-acyl isourea intermediates that undergo nucleophilic aza-Michael reaction or halogen displacement, respectively, followed by a final N→O acyl migration step (Scheme 1).[14]

In some cases, the N→O acyl migration process was competitive with the nucleophilic step, leading to the corresponding *N*-acylureas **4** and **5**, which are frequently found byproducts in the condensation reaction of carboxylic acids promoted by carbodiimides, alone or in a mixture with **3**. It is worth noting that this process is facilitated when the substituents on the carbodiimides are different in terms of electronic properties (highly asymmetric carbodiimides) rather than steric bulkiness (weakly asymmetric carbodiimides).[14b] However, *N*-acylureas **4** or **5** could be easily cyclized to the target hydantoins by treatment with NaH in

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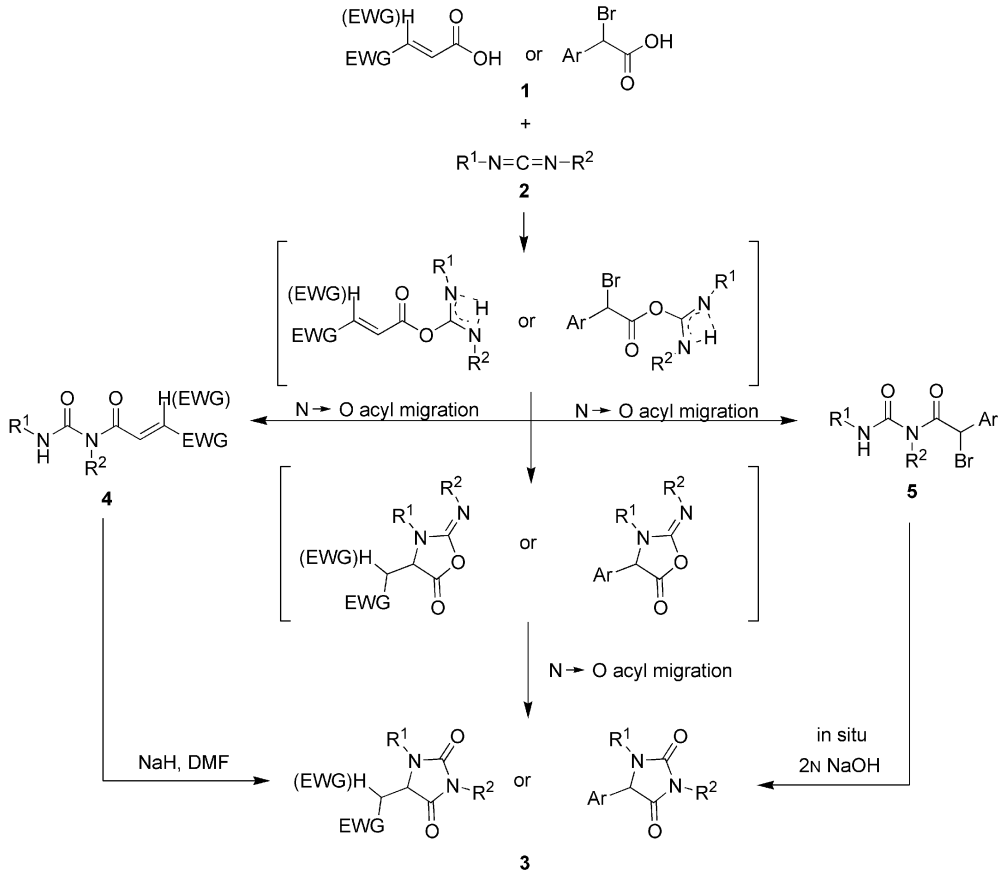
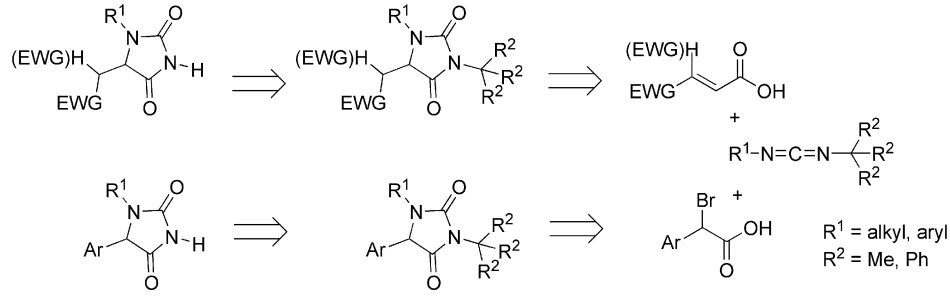


Scheme 1. One-pot, domino processes leading to 1,3,5-trisubstituted hydantoins.

THF or DMF, or in situ in a one-pot sequential process with a 2 N aqueous NaOH solution, respectively. Despite the great interest in the development of novel methodologies for the synthesis of hydantoins, there are only very few practical methods available in the literature for the synthesis of selectively 1,5-disubstituted hydantoins. The most utilized strategy relies on a four-step reaction sequence involving (1) the synthesis of the 1,3-unsubstituted hydantoin ring, (2) protection of the more reactive N-3 position, which usually arises with modest yields, (3) alkylation of the N-1 position and (4) removal of the N-3 protecting group.[15] In general, the above strategy reduces the yields, is time consuming and is not applicable for the synthesis of hydantoins with secondary alkyl groups or aromatic substituents at the N-1 position. Alternatively, 1,5-disubstituted hydantoins could be prepared by reaction between cyanate and *N*-alkyl amino acid esters followed by acid-catalyzed cyclization[16] or by treatment of freshly prepared aldimines with cyanide, cyanate and aqueous acid, in sequence.[17] Very recently, a new approach involving a three-step procedure for the synthesis of N-1 substituted hydantoins was reported, namely, amination of cyanogen bromide, alkylation of the resulting N-substituted cyanamide with methyl bromoacetate and final acid-catalyzed cyclization.[18] Although efficient and high yielding, this procedure envisages the use of highly toxic cyanogen bromide and leads to the formation of 5-unsubstituted hydantoins. In this paper, we wish to report a mild and efficient method for the synthesis of selectively 1,5-disubstituted hydantoins starting from easily available starting materials through a two-step reaction sequence in-



Scheme 2. Retrosynthetic scheme for the synthesis of 1,5-disubstituted hydantoins.

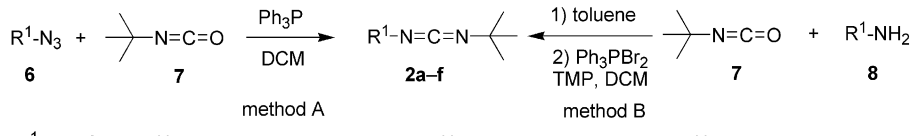
volving (1) the highly regiospecific domino condensation/aza-Michael (nucleophilic substitution)/O→N acyl migration with *N*-*tert*-butyl- or *N*-tritylcarbodiimides, leading to the regioselective formation of the corresponding *N*-3-*tert*-butyl or -trityl-substituted hydantoins and (2) selective cleavage of the tertiary alkyl N-3 protecting group (Scheme 2).

Results and Discussion

In previous work,[14] we demonstrated that asymmetric carbodiimides, namely, carbodiimides having different functionalities at the nitrogen atoms in terms of nucleophilic character and/or steric bulkiness, react with suitable carboxylic acids, giving rise to the formation of hydantoins with total regioselectivity in most cases. In particular, good results both in terms of regioselectivity and yield were obtained by using *N*-*tert*-butyl-substituted carbodiimides when the substituent at the other nitrogen atom was a primary alkyl group (benzyl substituent), leading to the formation of 1,3,5-trisubstituted hydantoins having the imine nitrogen atom protected with the removable *tert*-butyl substituent. Thus, we decided to further explore the reactivity of such *N*-*tert*-butylcarbodiimides to pave the way, after deprotection, to the selective synthesis of 1,5-disubstituted hydantoins with different substituents at the N-1 position, including secondary alkyl and aromatic groups. In particular, we synthesized suitable *N*-*tert*-butylcarbodiimides **2a**–**f** having primary, secondary and aryl substituents at the other nitrogen atom by a Staudinger reaction[19] between alkyl or aryl azides **6** and commercially available *tert*-butyl isocyanate (**7**) (Scheme 3, method A) or by dehydration of the corresponding ureas obtained by addition of amines or anilines **8** to **7** (Scheme 3, method B).[20] It is worth noting that these carbodiimides are quite stable and could be easily recovered in good yields by short-path flash chromatography (see Experimental Section).

Highly activated acid **1a** reacted smoothly with *tert*-butyl-substituted carbodiimides **2a**,**b** in DCM at room temperature without the need of a base, giving rise in a few minutes to the formation of N-1 primary alkyl or N-1 secondary alkyl *N*-3-*tert*-butyl-substituted hydantoins **3a**,**b**, respectively, as the only regioisomers (Table 1, Entries 1 and 2). Despite the fact that nitrogen-bearing aryl substituents are, in general, less nucleophilic than those bearing an alkyl group, the process was regioselective also with carbodiimide **2c**, which when reacted with **1a** under the same conditions, afforded exclusively hydantoin **3c**, although the process was slower (overnight; Table 1, Entry 3). Also, less-activated monoethyl fumarate **1b** when treated with dialkylcarbodiimides **2a**,**b**,**d**, in DCM led to a regioselective process, producing hydantoins **3d**,**e**,**f**, respectively, bearing the *tert*-butyl substituent in the 3-position (Table 1,Entries 4–6). When **1b** was treated with *N*-phenyl-*N*′-*tert*-butylcarbodiimide (**2c**) we obtained an equimolecular mixture of the expected hydantoin **3g** and *N*-acylurea derivative **4g** (Table 1, Entry 7).[21] The latter result is not surprising, as the two substituents in **2c** (an aryl and an alkyl substituent) possess different electronic features (strongly asymmetric carbodiimide). In order to increase the nucleophilicity of the intermediate *O*-acylurea, and thus the yield of **3g**, we performed the reaction in the presence of a base such as 2,4,6-trimethylpyridine (TMP). However, in this case, the base promoted the O→N acyl migration process, leading to the formation of a 3:1 mixture of *N*-acylurea **4g** and **3g** (Table 1, Entry 8). As expected, also 4,4,4-trifluoro-3-trifluoromethyl(Tmf)-crotonic acid (**1c**) gave the formation of hydantoins **3h**–**k** with total regiocontrol when treated with dialkylcarbodiimides **2a**,**d**–**f** in very good yields (Table 1, Entries 9–12) under the optimized conditions for this acid (TMP, CH_3CN). However, with *N*-phenyl-*N*′-*tert*-butylcarbodiimide (**2c**), acid **1c** produced hydantoin **3l** only in low yield, although as the only regioisomer (Table 1, Entry 13). To our surprise, α-bromophenylacetic acid (**1d**), which reacted smoothly (TMP, DCM) with an *N*-*tert*-butylcarbodiimide bearing a primary alkyl group at the other nitrogen atom, such as **2a**, producing only regioisomer **3m** (Table 1, Entry 14), did not react at all under the same conditions with analogous carbodiimides bearing a secondary alkyl group (data not shown).

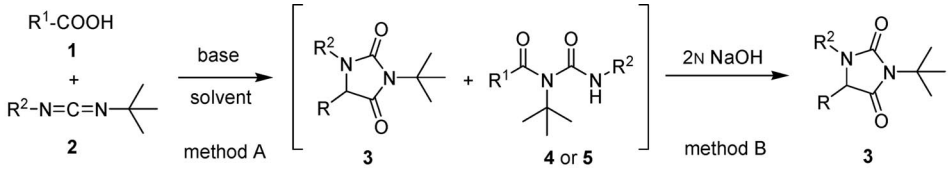
However, by performing the reaction in more polar dioxane, we obtained the selective formation of *N*-acylisourea **4n** as the only regioisomer in very good yield (Table 1, Entry 15). As expected,[14c] by treating the reaction mixture in situ with aqueous 2 N NaOH for a few minutes we obtained the selective formation of hydantoin regioisomers **3n**,**o** (**3o** in an equimolar ratio of two diastereoisomers) with carbodiimides **2e**,**f**, respectively (Table 1, Entries 16 and 17). When **1d** was treated with **2c** in dioxane in the presence of TMP, we obtained a mixture of hydantoin **3p** and *N*-acylurea **4p** together with other unidentified byproducts (Table 1, Entry 18), whereas cyclization with aqueous 2 N NaOH failed, leading to a complex mixture of byproducts (data not shown). Finally, when dialkylcarbodiimides **2a**,**b** were treated with poorly reactive aryl γ-oxo-α,β unsaturated carboxylic acids **1e**,**f** in DMF in the presence of TMP, we



R^1 = $PhCH_2$ (69%, **2a**, method B), cyclohexyl (65%, **2b**, method A), phenyl (83%, **2c**, method A), allyl (65%, **2d**, method B), cyclopentyl (69%, **2e**, method A), 2-Ph-ethyl (71%, **2f**, method A)

Scheme 3. Synthesis of *N*-*tert*-butyl-substituted carbodiimides.

Table 1. Synthesis of *N*-3 *tert*-butyl-substituted hydantoins.



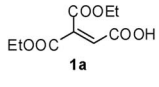
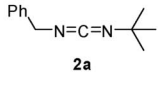
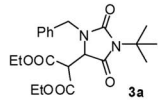
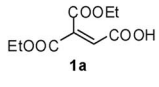
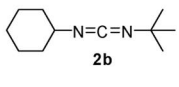
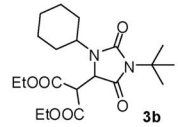
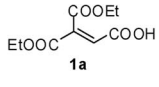
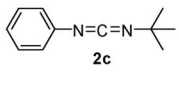
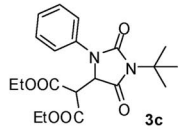
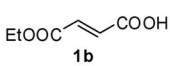
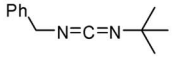
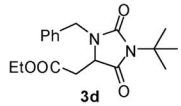
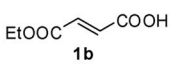
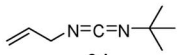
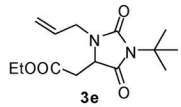
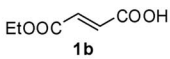
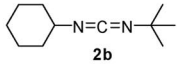
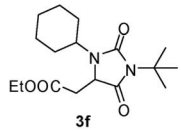
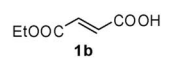
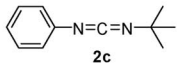
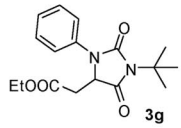
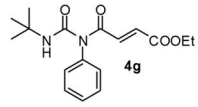
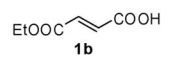
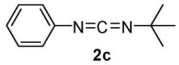
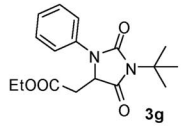
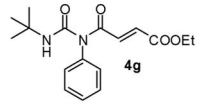
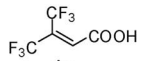
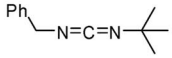
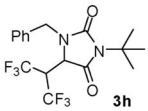
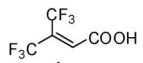
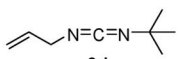
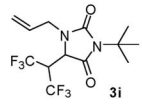
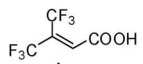
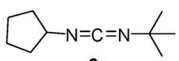
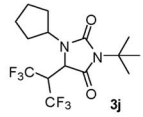
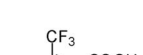
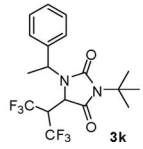
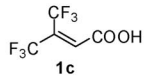
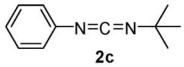
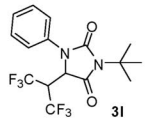
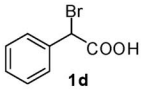
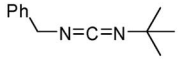
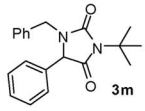
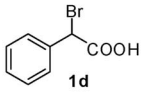
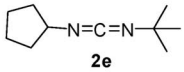
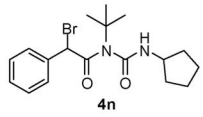
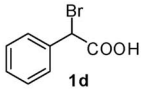
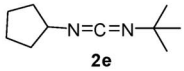
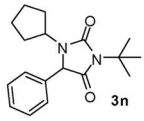
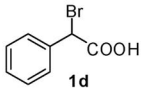
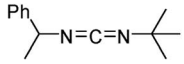
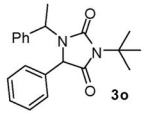
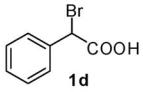
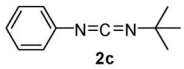
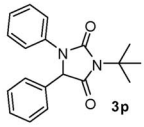
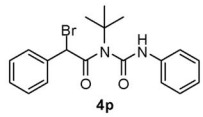
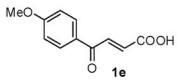
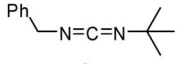
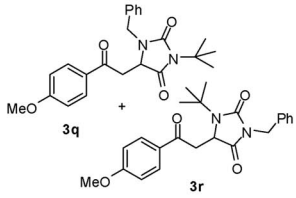
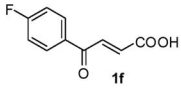
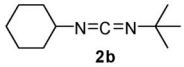
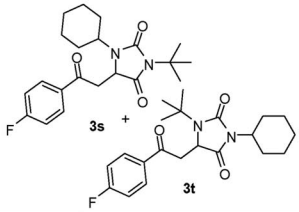
Entry	Carboxylic acid	Carbodiimide	Base	Solvent	Method	Hydantoin	*N*-acylurea	Ratio	Yield [%]
1[a]	 **1a**	 **2a**	none	DCM	A	 **3a**	/	100:0	65[b]
2	 **1a**	 **2b**	none	DCM	A	 **3b**	/	100:0	67[b]
3	 **1a**	 **2c**	none	DCM	A	 **3c**	/	100:0	63
4[a]	 **1b**	 **2a**	none	DCM	A	 **3d**	/	100:0	63
5	 **1b**	 **2d**	none	DCM	A	 **3e**	/	100:0	72
6	 **1b**	 **2b**	none	DCM	A	 **3f**	/	100:0	64
7	 **1b**	 **2c**	none	DCM	A	 **3g**	 **4g**	50:50	73
8	 **1b**	 **2c**	TMP	DCM	A	 **3g**	 **4g**	25:75	78
9[a]	 **1c**	 **2a**	TMP	CH_3CN	A	 **3h**	/	100:0	77
10	 **1c**	 **2d**	TMP	CH_3CN	A	 **3i**	/	100:0	76
11	 **1c**	 **2e**	TMP	CH_3CN	A	 **3j**	/	100:0	78
12	 **1c**	 **2f**	TMP	CH_3CN	A	 **3k**	/	100:0	75 [c]

Table 1. *(Conntinued)*

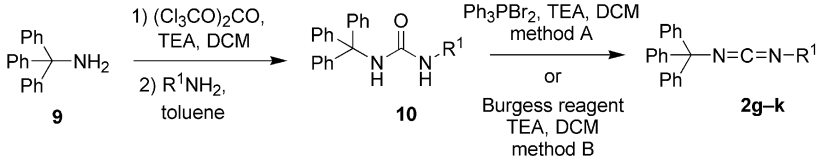
Entry	Carboxylic acid	Carbodiimide	Base	Solvent	Method	Hydantoin	*N*-acylurea	Ratio	Yield [%]
13	 **1c**	 **2c**	TMP	CH_3CN	A	 **3l**	/	100:0	27
14[d]	 **1d**	 **2a**	TMP	DCM	A	 **3m**	/	100:0	83
15	 **1d**	 **2e**	TMP	dioxane	A	/	 **4n**	0:100	74
16	 **1d**	 **2e**	TMP	dioxane	B	 **3n**	/	100:0	71
17	 **1d**	 **2f**	TMP	dioxane	B	 **3o**	/	100:0	85[e]
18	 **1d**	 **2c**	TMP	dioxane	A	 **3p**	 **4p**	50:50	n.d.[f]
19[a]	 **1e**	 **2a**	TMP	DMF	A	 **3q** + **3r**	/	100:0	92[g]
20	 **1f**	 **2b**	TMP	DMF	A	 **3s** + **3t**	/	100:0	73[g]

[a] See Ref.[14b] [b] Reaction was complete in 5 min. [c] Two diastereoisomers in a ca. 5:1 ratio. [d] See Ref.[14c] [e] Equimolar ratio of two diastereoisomers. [f] Not determined. [g] Equimolar ratio of regioisomers.

obtained an equimolecular mixture of hydantoin regioisomers **3q**,**r** and **3s**,**t**, respectively, in very good yields (Table 1, Entries 19 and 20).

Next, in order to increase the difference between the two nitrogen atoms both in terms of nucleophilic power and steric bulkiness in the *O*-acylisourea intermediates, we decided to study the behaviour of related *N*-trityl-substituted carbodiimides **2g**–**k** with the expectation that the regioselectivity of the process would increase in those cases where *N*-*tert*-butylcarbodiimides failed (for instance, with acids **1e**,**f**). Such carbodiimides could be easily obtained by dehydration promoted by freshly prepared Ph_3PBr_2[20] or by Burgess reagent[22] of the corresponding ureas **10**. The latter can be obtained by addition of alkyl or arylamines to trityl-isocyanate, which was synthesized by reaction of commercially available tritylamine (**9**) with triphosgene (Scheme 4). Also in this case, the resulting carbodiimides were easily recovered by short-path flash chromatography.

Highly activated acid **1a** reacted smoothly also with N-primary and secondary alkyl, *N*′-tritylcarbodiimides **2g**,**h**, leading to hydantoins **3aa**,**ab** as the only regioisomers (Table 2, Entries 1 and 2), whereas no reaction occurred with *N*-phenyl-*N*′-tritylcarbodiimide (**2i**) (Table 2, Entry 3), probably due to the lower reactivity of the carbodiimide compared with the corresponding *tert*-butylcarbodiimide **2c**, which in turn is probably due to lower electrophilicity

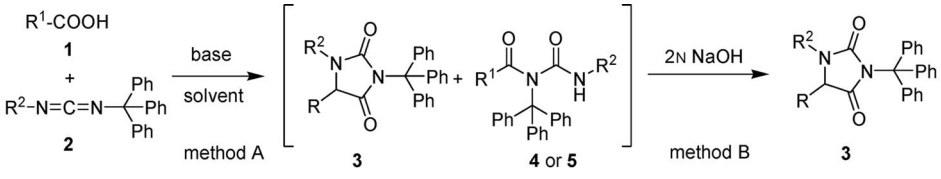


R^1 = *n*-butyl (78%, **2g**, method A), isopropyl (69%, **2h**, method A), phenyl (92%, **2i**, method B), benzyl (73%, **2j**, method A), 4-methoxyphenyl (91%, **2k**, method B)

Scheme 4. Synthesis of *N*-trityl-substituted carbodiimides.

rather than higher steric hindrance. *N*-Tritylcarbodiimides were less reactive than the corresponding *N*-*tert*-butyl derivatives also in the intramolecular nucleophilic step. In fact, when **2j** was treated with carboxylic acid **1b** we obtained the almost exclusive formation of *N*-acylurea **4ac** as the only regioisomer in good yield, whereas when treated with **2h**, which has a nitrogen atom bearing a secondary alkyl group and thus more nucleophilic, we obtained the regioselective formation of a 3:1 mixture of *N*-acylurea **4ad** and hydantoin **3ad** (Table 2, Entries 4 and 5).[23] Not surprisingly, the ratio of hydantoin **3ae** versus *N*-acyl derivative **4ae** increased, becoming the predominant product, when **1b** was treated with *N*-phenyl-*N*′-tritylcarbodiimide (**2i**). As a matter of fact, such a carbodiimide is more "symmetric" compared with **2h**,**j** as a result of the electronic features of the trityl group, which are much closer to those of an aryl substituent rather than an alkyl one. Acid **1c** reacted smoothly also with *N*-tritylcarbodiimides **2j**,**h** to produce hydantoins **3af**,**ag**, respectively, in very good yields and total regioselectivity (Table 2, Entries 7 and 8). However, the same acid did not react at all with **2i**, confirming the low reactivity of this acid with less reactive carbodiimides such **2c** and **2i** (Table 2, Entry 9). The reactivity of α-bromophenylacetic acid (**1d**) with *N*-tritylcarbodiimides was very similar to that observed with the corresponding *N*-*tert*-butylcarbodiimides, leading to a clean reaction with carbodiimides bearing a primary alkyl group such as **2j** (Table 2, Entry 11) and a mixture of hydantoin **3ai**, *N*-acylurea **4ai** and other byproducts with carbodiimide **2i** (Table 2, Entry 12). Unexpectedly, aryl γ-oxo-α,β unsaturated carboxylic acids **1e**,**f** reacted with *N*-tritylcarbodiimides in a chemo- and regioselective way. In fact, reactions of *N*-primary and secondary alkyl, *N*′-tritylcarbodiimides **2g**,**h** with **1e**,**f** produced the formation of hydantoins **3aj** and **3al**, respectively, as the only regioisomers (Table 2, Entries 12 and 14). Also, *N*-aryl-*N*′-tritylcarbodiimides **2i**,**k** produced completely chemoselective processes when reacted with acids **2g**,**h**, leading to the corresponding hydantoins (Table 2, Entries 13, 15, and 16) although to achieve good yield the reactions were run for 24 h at 80 °C. However, in the latter cases, the process was not completely regioselective. In fact, when **1e**,**f** were treated with carbodiimide **2k**, bearing a *para*-methoxyphenyl N-substituent, we still obtained a highly regioselective process leading to the formation of hydantoins **3ak** and **3an** as major regioisomers with 82 and 78% regioisomeric excesses, respectively (Table 2, Entries 13 and 16), whereas with less nucleophilic carbodiimide **2i**, bearing an *N*-phenyl substituent, the regioselectivity dropped down to 60% (Table 2, Entry 15). However, the latter results strongly improve the synthetic methodology, as

Table 2. Synthesis of *N*-3 trityl-substituted hydantoins.



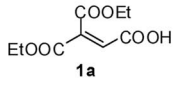
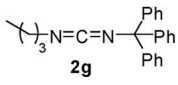
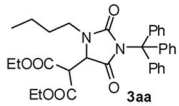
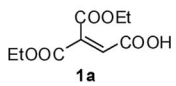
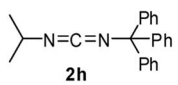
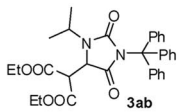
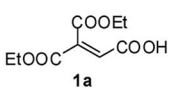
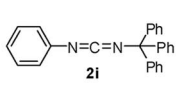
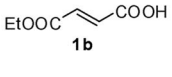
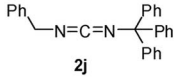
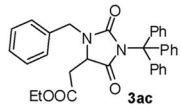
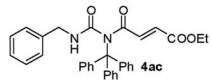
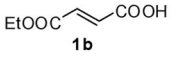
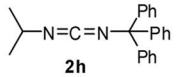
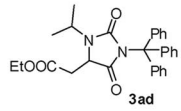
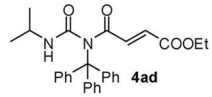
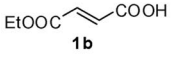
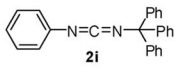
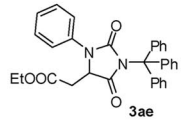
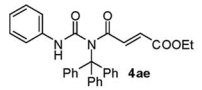
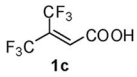
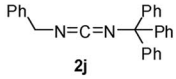
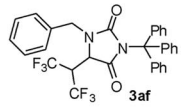
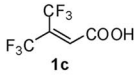
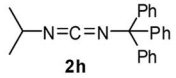
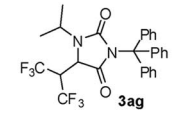
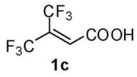
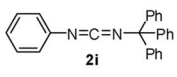
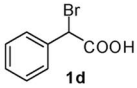
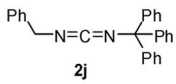
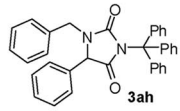
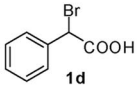
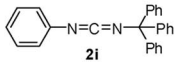
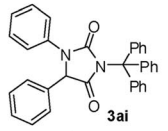
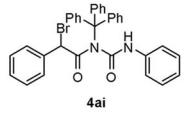
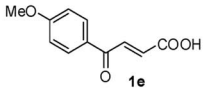
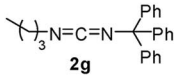
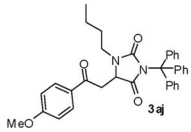
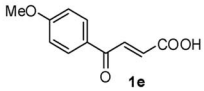
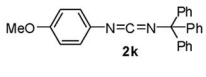
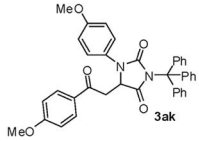
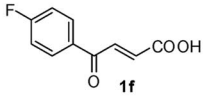
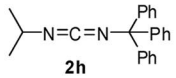
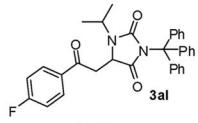
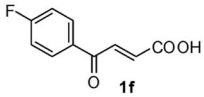
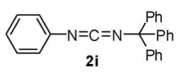
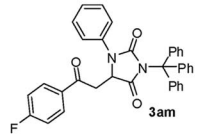
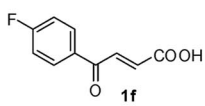
Entry	Carboxylic acid	Carbodiimide	Base	Solvent	Method	Hydantoin	*N*-acylurea	Ratio	Yield [%]
1	 **1a**	 **2g**	none	DCM	A	 **3aa**	/	100:0	65
2	 **1a**	 **2h**	none	DCM	A	 **3ab**	/		63
3	 **1a**	 **2i**	none	DCM	A	/	/		n.r[a]

Table 2. *(Conntinued)*

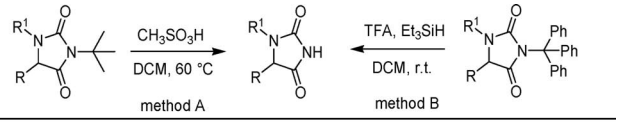
Entry	Carboxylic acid	Carbodiimide	Base	Solvent	Method	Hydantoin	*N*-acylurea	Ratio	Yield [%]
4	 **1b**	 **2j**	none	DCM	A	 **3ac**	 **4ac**	5:95	75
5	 **1b**	 **2h**	none	DCM	A	 **3ad**	 **4ad**	25:75	65
6	 **1b**	 **2i**	none	DCM	A	 **3ae**	 **4ae**	89:11	64
7	 **1c**	 **2j**	TMP	CH_3CN	A	 **3af**	/	100:0	78
8	 **1c**	 **2h**	TMP	CH_3CN	A	 **3ag**	/	100:0	79
9	 **1c**	 **2i**	TMP	CH_3CN	A	/	/	/	n.r.
10	 **1d**	 **2j**	TMP	DCM	A	 **3ah**	/	100:0	81
11	 **1d**	 **2i**	TMP	dioxane	B	 **3ai**	 **4ai**	50:50	n.d.[b]
12	 **1e**	 **2g**	TMP	DMF	A	 **3aj**		100:0	85
13	 **1e**	 **2k**	TMP	DMF	A	 **3ak**	/	100:0	67[c,d]
14	 **1f**	 **2h**	TMP	DMF	A	 **3al**	/	100:0	76
15	 **1f**	 **2i**	TMP	DMF	A	 **3am**	/	100:0	63[c,e]
16	 **1f**	**2k**	TMP	DMF	A	**3an**	/	100:0	67[c,f]

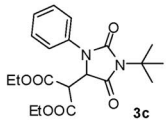
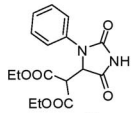
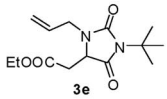
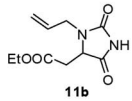
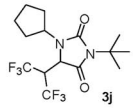
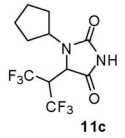
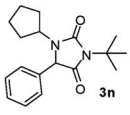
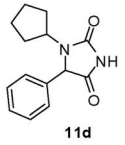
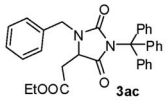
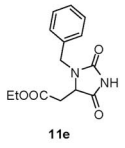
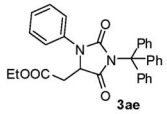
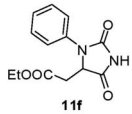
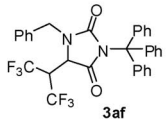
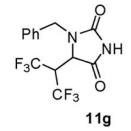
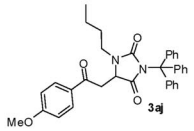
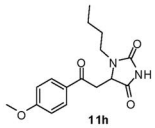
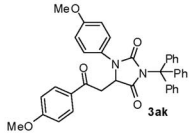
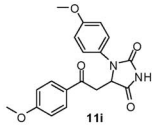
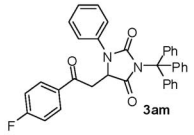
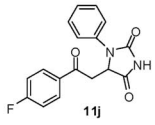
[a] No reaction occurred. [b] Not determined. [c] Reaction performed in 24 h at 80 °C in a sealed tube. [d] A 10:1 mixture of the two regioisomers was obtained. [e] A 4:1 mixture of the two regioisomers was obtained. [f] An 8:1 mixture of the two regioisomers was obtained.

aryl γ-oxo-α,β unsaturated carboxylic acids reacted with *N*-*tert*-butylcarbodiimides with no regiocontrol in all cases.

Finally, in order to validate our strategy, a series of hydantoins **2** were selectively deprotected at the nitrogen atom in the 3-position of the ring, leading to a library of the target 1,3-disubstitued hydantoins **11**. For this purpose, hydantoins bearing the *tert*-butyl substituent were treated with a 10% solution of methansulfonic acid in DCM at 60 °C in a sealed tube for several hours, leading to the formation of products **11a–d** in very good yields (Table 3, Entries 1–4). The corresponding *N*-trityl derivatives were converted into target products **11e–j** in excellent yield by treatment with a 10% solution of TFA in DCM, in the presence of Et_3SiH at room temperature (Table 3, Entries 5–10).

Table 3. Synthesis of 1,5-disubstituted hydantoins.



Entry	Hydantoin	Method	Product	Yield [%]
1	 **3c**	A	 **11a**	93
2	 **3e**	A	 **11b**	89
3	 **3j**	A	 **11c**	93
4	 **3n**	A	 **11d**	91
5	 **3ac**	B	 **11e**	92
6	 **3ae**	B	 **11f**	87
7	 **3af**	B	 **11g**	85
8	 **3aj**	B	 **11h**	85
9	 **3ak**	B	 **11i**	87
10	 **3am**	B	 **11j**	100

Conclusions

In summary, we have developed a general, straightforward method for the preparation of 1,5-disubstituted hydantoins in good to excellent yields through a two-step strategy relying on a highly regioselective domino reaction between *N*-*tert*-butyl- or *N*-trityl-substituted carbodiimides and activated α,β-unsaturated carboxylic acids or α-haloarylacetic acids followed by selective deprotection of the tertiary alkyl substituent at the 3-position of the ring. In general, we suggest the use of *N*-*tert*-butylcarbodiimides because they are easier to prepare (by Staudinger reaction) and gave cleaner reactions. However, in some cases, when the carboxylic acids are less reactive like aryl γ-oxo-α,β unsaturated carboxylic acids, with such carbodiimides the process is not selective, producing a mixture of the two hydantoin regioisomers. In these cases, the use of related *N*-tritylcarbodiimides overcame this drawback, leading to the formation of the desired hydantoins as the only regioisomers when the other carbodiimide substituent is a primary or secondary alkyl group, or as major regioisomers with *N*-aryl-*N*′-tritylcarbodiimides. A large array of 1,5-disubstituted hydantoins with primary, secondary, cyclic and aryl groups at the 1-position can be synthesized through this method that overcomes the drawbacks of precedent methodologies (harsh conditions or toxic reagents). For these reasons, our strategy looks particularly suitable for solid-phase/combinatorial chemistry. The latter issue, as well as the development of a stereoselective version of the domino process, are currently in progress in our laboratory.

Experimental Section

General Methods: Commercially available reagent-grade solvents were employed without purification. ^{1}H NMR spectra were run on spectrometers at 250, 400 or 500 MHz. Chemical shifts are expressed in ppm (δ), using tetramethylsilane (TMS) as internal standard for ^{1}H and ^{13}C nuclei (δ_H and δ_C = 0.00 ppm), whereas C_6F_6 was used as an external standard (δ_F = 162.90 ppm) for ^{19}F nuclei.

Materials: Carbodiimides were prepared according to the literature (see in the manuscript). 4,4,4-Trifluoro-3-Tmf-crotonic acid (**1c**) and α-bromophenylacetic acid (**1d**) are commercially available, whereas acids **1a**,**b**,**e**,**f** were prepared as reported in ref.[14b] ^{1}H NMR and ^{13}C NMR spectroscopic data of carbodiimides **2c**,[24] **2i**[22] and **2f**[25] were in agreement with those previously reported.

General Procedure for the Synthesis of Tetrasubstituted Hydantoins 3: To a stirred solution of acid **1** (1 equiv.) in organic solvent (0.1 M solution) was added carbodiimide **2** (1 equiv. or 1.5 equiv. for acid **1d**) followed by TMP (1 equiv.) at room temperature, and the mix-

ture was stirred overnight (unless otherwise noted). When needed (see Tables 1 and 2), aqueous 2 N NaOH (10% in volume) was added, and the mixture was stirred for 15 min. Aqueous 1 N HCl was added until acidic pH, and the resulting mixture was extracted with DCM. The combined organic layer was dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by flash chromatography.

Diethyl 2-(1-*tert*-Butyl-3-cyclohexyl-2,5-dioxoimidazolidin-4-yl)malonate (3b): R_f = 0.53 (hexane/AcOEt, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.27 (d, J = 4.2 Hz, 1 H), 4.14 (m, 4 H), 3.86 (d, J = 4.2 Hz, 1 H), 3.56 (m, 1 H), 1.63 (m, 6 H), 1.51 (s, 9 H), 1.21 (t, J = 7.3 Hz, 3 H), 1.19 (t, J = 7.8 Hz, 3 H), 1.16 (m, 2 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 171.3, 168.9, 157.3, 62.2, 61.7, 56.6, 53.5, 53.2, 31.3, 30.2, 28.5, 25.9, 25.2, 14.1, 14.0 ppm. MS (ESI): *m*/*z* (%) = 397.1 (22) [M$^+$ + H], 419.1 (100) [M$^+$ + Na], 435.1 (14) [M$^+$ + K].

Diethyl 2-(3-Butyl-2,5-dioxo-1-tritylimidazolidin-4-yl)malonate (3aa): R_f = 0.39 (hexane/AcOEt, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (m, 6 H), 7.16–7.14 (m, 9 H), 4.24 (d, J = 2.6 Hz, 1 H), 4.19–4.12 (m, 4 H), 4.00 (d, J = 2.6 Hz, 1 H), 3.52 (m, 1 H), 2.94 (m, 1 H), 1.36 (m, 2 H), 1.22 (t, J = 7.0 Hz, 3 H), 1.17 (t, J = 7.0 Hz, 3 H), 0.98 (m, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 170.3, 166.9, 165.6, 156.2, 142.4, 128.6, 127.3, 126.5, 74.0, 62.3, 62.1, 57.3, 52.8, 41.5, 29.0, 19.4, 13.95, 13.96, 13.5 ppm. MS (ESI): *m*/*z* (%) = 579.2 (100) [M$^+$ + Na], 557.1 (8) [M$^+$ + H].

General Procedure for *N*-*tert*-Butyl Deprotection: A stirred solution of hydantoin **3** (1 equiv.) and CH_3SO_3H (10% in volume) in DCM (0.5 M solution) was heated at 60 °C in a sealed tube for 3 h. The solution was cooled to room temperature, diluted with aqueous 5% $NaHCO_3$ until basic and extracted with DCM. The combined organic layer was dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. When necessary, the crude was purified by flash chromatography.

Diethyl 2-(2,5-Dioxo-3-phenylimidazolidin-4-yl)malonate (11a): R_f = 0.34 (hexane/AcOEt, 60:40). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.64 (br. s, 1 H), 7.34–7.28 (m, 5 H), 5.16 (d, J = 4.2 Hz, 1 H), 4.28 (q, J = 7.0 Hz, 2 H), 4.11 (m, 2 H), 3.92 (d, J = 4.2 Hz, 1 H), 1.30 (t, J = 7.0 Hz, 3 H), 1.18 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 169.9, 165.5, 165.4, 154.4, 134.4, 129.5, 126.9, 123.8, 62.6, 62.1, 60.3, 50.9, 13.9, 13.8 ppm. MS (ESI): *m*/*z* (%) = 335.0 (6) [M$^+$ + H], 357.0 (100) [M$^+$ + Na].

General Procedure for *N*-Trityl Deprotection: A solution of hydantoin **3** (1 equiv.), Et_3SiH (4 equiv.) and TFA (10% in volume) in DCM (0.5 M solution) was stirred at room temperature until all the starting material was consumed (TLC monitoring). The solution was diluted with aqueous 5% $NaHCO_3$ until basic and extracted with DCM. The combined organic layer was dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum, and the crude was purified by flash chromatography.

Ethyl 2-(3-Benzyl-2,5-dioxoimidazolidin-4-yl)acetate (11e): R_f = 0.24 (hexane/AcOEt, 50:50). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (br. s, 1 H), 7.33 (m, 5 H), 4.77 (d, J = 15.6 Hz, 1 H),4.30 (d, J = 15.6 Hz, 1 H),4.14 (t, J = 4.8 Hz, 1 H), 4.08 (m, 2 H), 2.78 (d, J = 4.8 Hz, 2 H), 1.19 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 172.4, 168.9, 135.8, 129.0, 128.2, 128.1, 61.4, 57.3, 45.1, 34.1, 14.0 ppm. MS (ESI): *m*/*z* (%) = 277.2 [M$^+$+H, (100)].

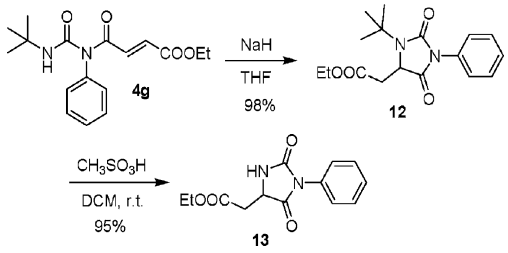
Supporting Information (see footnote on the first page of this article): The spectroscopic data for all the remaining compounds and the copies of the ^{1}H and ^{13}C NMR spectra for all new compounds.

Acknowledgments

Politecnico di Milano (Progetto Giovani Ricercatori 2007–2008) is gratefully acknowledged for economic support.

[1] J. C. Thenmozhiyal, P. T. H. Wong, W. K. Chui, *J. Med. Chem.* **2004**, *47*, 1527–1535.
[2] a) C. W. Bazil, T. A. Pedley, *Annu. Rev. Med.* **1998**, *49*, 135–162; b) M. S. Luer, *Neurol. Res.* **1998**, *20*, 178–182.
[3] a) M. Matsukura, Y. Daiku, K. Ueda, S. Tanaka, T. Igarashi, N. Minami, *Chem. Pharm. Bull.* **1992**, *40*, 1823–1827; b) J. Knabe, J. Baldauf, A. Ahlhelm, *Pharmazie* **1997**, *52*, 912–919.
[4] L. Somsák, L. Kovács, M. Tóth, E. Ösz, L. Szilágyi, Z. Györgydeák, Z. Dinya, T. Docsa, B. Tóth, P. Gergely, *J. Med. Chem.* **2001**, *44*, 2843–2848.
[5] a) G. P. Moloney, A. D. Robertson, G. R. Martin, S. MacLennan, N. Mathews, S. Dosworth, P. Y. Sang, C. Knight, R. Glen, *J. Med. Chem.* **1997**, *40*, 2347–2362; b) G. P. Moloney, G. R. Martin, N. Mathews, A. Milne, H. Hobbs, S. Dosworth, P. Y. Sang, C. Knight, M. Williams, M. Maxwell, R. Glen, *J. Med. Chem.* **1999**, *42*, 2504–2526.
[6] M. Jansen, H. Potschka, C. Brandt, W. Löscher, G. Dannhardt, *J. Med. Chem.* **2003**, *46*, 64–73.
[7] K. Last-Barney, W. Davidson, M. Cardozo, L. L. Frye, C. A. Grygon, J. L. Hopkins, D. D. Jeanfavre, S. Pav, C. Qian, J. M. Stevenson, L. Tong, R. Zindell, T. A. Kelly, *J. Am. Chem. Soc.* **2001**, *123*, 5643–5650.
[8] J. C. Sutherland, G. P. Hess, *Nat. Prod. Rep.* **2000**, *17*, 621–631.
[9] a) C. Syldatk, R. Müller, M. Siemann, K. Krohn, F. Wagner, *Biocatalytic Production of Amino Acids and Derivatives*, Hanser, München, **1992**, p. 75; b) K. Drauz, H. Waldmann, *Enzyme Catalysis in Organic Synthesis*, VCH, Weinheim, **1995**, p. 409.
[10] C. A. López, G. G. Trigo, *Adv. Heterocycl. Chem.* **1985**, *38*, 177–228.
[11] a) S. W. Kim, S. Y. Ahn, J. S. Koh, J. H. Lee, S. Ro, H. Y. Cho, *Tetrahedron Lett.* **1997**, *38*, 4603–4606; b) J. Matthews, R. A. Rivero, *J. Org. Chem.* **1997**, *62*, 6090–6092; c) M. M. Sim, A. Ganesan, *J. Org. Chem.* **1997**, *62*, 3230–3235.
[12] A. Boeijen, J. A. W. Kruijtzer, R. M. Liskamp, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2375–2380.
[13] a) B. A. Dressman, L. A. Spangle, S. W. Kaldor, *Tetrahedron Lett.* **1996**, *37*, 937–940; b) K. H. Park, M. J. Kurth, *Tetrahedron Lett.* **2000**, *41*, 7409–7413; c) M. Lamothe, M. Lannuzel, M. Perez, *J. Comb. Chem.* **2002**, *4*, 73–78; d) A. Nefzi, M. Giulianotti, L. Troung, S. Rattan, J. M. Ostresh, R. A. Houghten, *J. Comb. Chem.* **2002**, *4*, 175–178; e) J. Vázquez, M. Royo, F. Albericio, *Lett. Org. Chem.* **2004**, *1*, 224–226; f) C. Hulme, L. Ma, J. J. Romano, G. Morton, S. Y. Tang, M. P. Cherrier, S. Choi, J. Salvino, R. Labaudiniere, *Tetrahedron Lett.* **2000**, *41*, 1889–1893; g) M. Meusel, A. Ambrożak, T. K. Hecker, M. Gütschow, *J. Org. Chem.* **2003**, *68*, 4684–4692; h) M. Beller, M. Eckert, W. A. Moradi, H. Neumann, *Angew. Chem. Int. Ed.* **1999**, *38*, 1454–1456; i) B. Zhao, H. Du, Y. Shi, *J. Am. Chem. Soc.* **2008**, *130*, 7220–7221.
[14] a) A. Volonterio, M. Zanda, *Tetrahedron Lett.* **2003**, *44*, 8549–8551; b) A. Volonterio, C. Ramirez de Arellano, M. Zanda, *J. Org. Chem.* **2005**, *70*, 2161–2170; c) F. Olimpieri, A. Volonterio, M. Zanda, *Synlett* **2008**, 3016–3020.
[15] O. O. Orazzi, R. A. Corral, *Experientia* **1965**, *21*, 508.
[16] a) J. A. Monn, M. J. Valli, S. M. Massey, R. A. Wright, C. R. Salhoff, B. G. Johnson, T. Howe, C. A. Alt, G. A. Rhodes, R. L. Robey, K. R. Griffey, J. P. Tizzano, M. J. Kallman, D. R. Helton, D. D. Schoepp, *J. Med. Chem.* **1997**, *40*, 528; b) J. A. Monn, M. J. Valli, S. M. Massey, M. M. Hansen, T. J. Kress, J. P. Wepsic, A. R. Harkness, J. L. Grutsch, R. A. Wright, B. G. Johnson, S. Andis, L. A. Kingston, R. Tomlinson, R. Lewis, K. R. Griffey, J. P. Tizzano, D. D. Schoepp, *J. Med. Chem.* **1999**, *42*, 1027; c) F. Tellier, F. Acher, I. Brabet, J. P. Pin, R. Azerad, *Bioorg. Med. Chem.* **1998**, *6*, 195.

[17] W. J. Brouillette, G. B. Brown, T. M. DeLorey, G. Liang, *J. Pharm. Sci.* **1990**, *79*, 871–874.
[18] V. Kumar, M. P. Kaushik, A. Mazumdar, *Eur. J. Org. Chem.* **2008**, 1910–1916.
[19] a) H. Staudinger, J. Meyer, *Helv. Chim. Acta* **1919**, *2*, 635–646; b) H. Staudinger, E. Hauser, *Helv. Chim. Acta* **1921**, *2*, 861.
[20] C. Palomo, R. Mestres, *Synthesis* **1981**, 373–374.
[21] The structure of **4g** was assessed by cyclization to hydantoin **12** and removal of the *tert*-butyl substituent with a 10% solution of CH_3SO_3H in DCM at room temperature.



[22] M. R. Barvian, H. D. H. Showalter, A. M. Doherty, *Tetrahedron Lett.* **1997**, *38*, 6799–6802.
[23] Also, in this cases the structures of *N*-acylureas **4ac** and **4ad** were determined by cyclization to the corresponding hydantoins **3ac** and **3ad**, respectively, promoted by NaH in THF.
[24] S.-I. Fujiwara, T. Matsuya, H. Maeda, T. Shin-ike, N. Kambe, N. Sonoda, *Synlett* **1999**, 75–76.
[25] Z. Crawczyk, C. Belzeki, *Pol. J. Chem.* **1979**, *53*, 631–641.

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