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Synthesis of 1,3,5-Trisubstituted Hydantoins by Regiospecific Domino Condensation/Aza-Michael/O→N Acyl Migration of Carbodiimides with Activated α,β-Unsaturated Carboxylic Acids†

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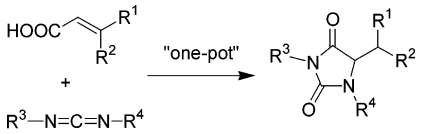

R^1 = EWG, R^2 = H, COOEt, CF_3
R^3 = alkyl or aryl, R^4 = alkyl or aryl

Carbodiimides and suitably activated α,β-unsaturated carboxylic acids react effectively to afford a vast array of 1,3,5-trisubstituted hydantoins by means of a regiospecific domino condensation/aza-Michael/N→O acyl migration. The reaction works well in very mild conditions (20 °C, dichloromethane) with fumaric acid derivatives bearing an electron-withdrawing group in the β position. Good results have been obtained also with less activated substrates bearing only one electron-withdrawing group in the β position, using more polar solvents (acetonitrile, DMF), and in the presence of a base (2,4,6-trimethylpyridine). Reactions with asymmetric carbodiimides are generally highly chemo- and regioselective, giving rise to the formation of a single regioisomeric hydantoin. However, asymmetric carbodiimides bearing one alkyl group and one aryl group can produce variable amounts of *N*-acylurea byproducts. The latter could be easily recovered and transformed into the corresponding hydantoins. A detailed study of the influence of key reaction parameters such as solvent, base, and structure of the reactants on the reaction outcome and mechanism is presented. This methodology is particularly convenient for the synthesis of trifluoromethyl-substituted hydantoins, which could be interesting as bioactive compounds in medicinal chemistry, as well as precursors of the corresponding α-amino acids.

Introduction

One of the challenges of medicinal chemistry is the promotion of the structural diversity of a ligand, which can be achieved by the attachment of pharmacophoric groups to the rigidified molecule. Small, substituted heterocyclic compounds offer a unique possibility of different kinds and degrees of substitution. In particular, 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

† This paper is dedicated to Prof. Pierfrancesco Bravo on the occasion of his 70th birthday.

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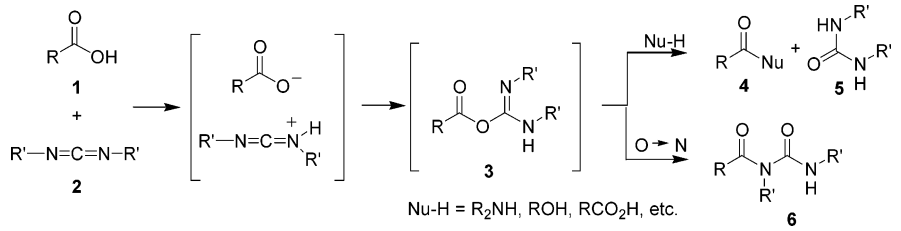
SCHEME 1. Mechanism of Carbodiimide Activation



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. For this reason, there is a lot of interest in developing new strategies for a straightforward synthesis of substituted hydantoins both in solution and in solid phase. Moreover, substituted hydantoins are important building blocks for the synthesis of nonnatural amino acids both in racemic form by alkaline hydrolytic degradation[8] and in an enantioselective way by enzymatic resolution.[9] 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 chorosulfonyl isocyanates, respectively, which requires extended reaction time or high temperature.[10] In this way, 3,5-di and 3,5,5-trisubstituted hydantoins are readily accessible, while 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 via Mitsunobu reaction.[12] However, different new methodologies for synthesizing 1,3,5-trisubstituted hydantoins have been recently reported, including a mild cyclization/cleavage approach to various linear urea compounds in solid phase,[11−13] a novel application of the Ugi five-component condensation,[14] a base-catalyzed rearrangement of 5-substituted barbituric acids,[15] and palladium-catalyzed carbonylation of aldehydes in the presence of urea derivatives.[16]

Carbodiimides[17] such as dicyclohexylcarbodiimide (DCC) and diisopropylcarbodiimide (DIC) are very popular reagents often used to activate carboxylic acid groups to nucleophilic substitution.[18] The mechanism and kinetics of reaction of carbodiimides with carboxylic acids have been extensively investigated.[19] The reaction sequence involves a proton transfer from the carboxylic acid **1** (Scheme 1) to the basic nitrogen of the carbodiimide **2**, followed by addition of the carboxylate to form the *O*-acyl isourea **3**.

It is known[19a] that in low dielectric constant solvents such as CH_2Cl_2 (DCM), formation of **3** occurs instantaneously and, in the absence of a nucleophile or a base, it can be stable for many hours. The intermediate **3** is a reactive species and in the presence of a nucleophile affords the coupling product **4**, together with a urea coproduct **5**. However, **3** can undergo a rearrangement, the so-called O→N acyl migration, to give the *N*-acylurea **6**, which is a frequently found byproduct in these reactions.

Very recently, we have developed a new straightforward method for the synthesis of 1,3,5-trisubstituted hydantoins by a one-pot domino[20] condensation/aza-Michael addition/O→N acyl migration of carbodiimides with activated α,β-unsaturated carboxylic acids, which proceeds under very mild conditions.[21] Different commercially available carbodiimides **2** (Scheme 2) react smoothly at 20 °C in DCM with fumaric and maleic acid derivatives **1** to give the intermediate *O*-acyl isourea **3**, which immediately produces the intermediate **7** through an intramolecular N-Michael addition.[22] The following

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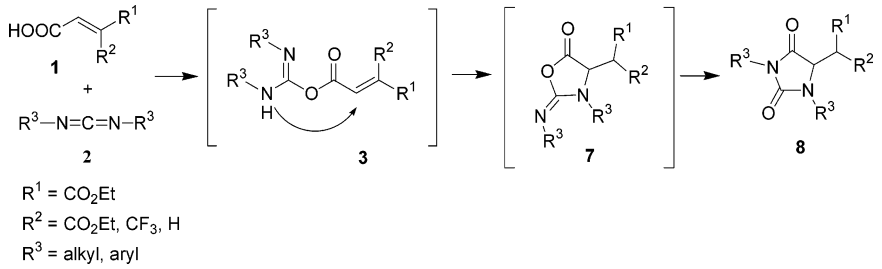
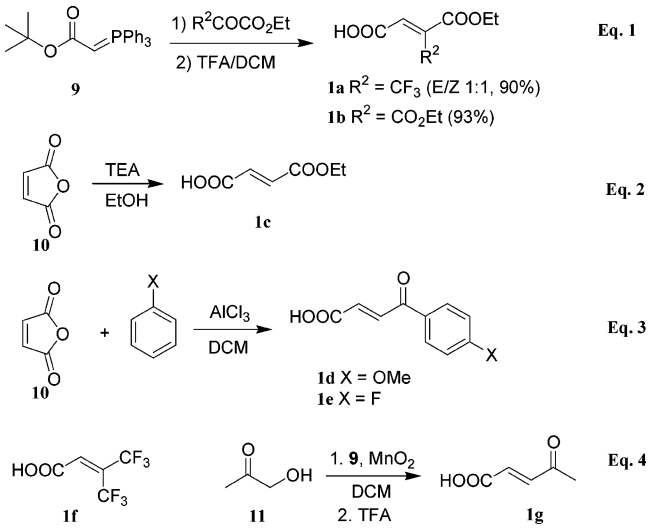
(22) For a related process involving an amino group as a nucleophile, see: (a) Saito, T.; Tsuda, K.; Saito, Y. *Tetrahedron Lett.* **1996**, *37*, 209−212. (b) Molina, P.; Aller, E.; Lorenzo, A. *Synthesis* **1998**, *26*, 283−287. A conceptually related process involving fumaric acid monoethylester and several carbodiimides, in the presence of alcohols or amines, was reported to produce rearranged urea products via the intermediates **3** and **7**. In that case, the corresponding hydantoins were occasionally observed as minor byproducts. See: (c) Kishikawa, K.; Sankhavasi, W.; Yoshizaki, K.; Kohmoto, S.; Yamamoto, M.; Yamada, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1205−1209. In this reference, no attempts to produce hydantoins and no description of the reaction course in the absence of alcohols or amines were described.

SCHEME 2 One-Pot Domino Condensation/Aza-Michael Addition/O→N Acyl Migration



SCHEME 3. Preparation of Starting Materials 1a−g



O→N acyl migration gives rise to the formation of the hydantoin **8**.

In this paper, we provide a full account on the scope and limits of this new methodology, which has been studied in detail by performing the reaction on many different α,β-unsaturated carboxylic acids having variable degrees of activation and carbodiimides, including hitherto scarcely investigated asymmetric carbodiimides having different substituents at the two nitrogen atoms. The new results dramatically expand the scope of the process and allow for the preparation of a potentially very large array of structurally diverse hydantoins.[23]

Results

Synthesis of α,β-Unsaturated Carboxylic Acids 1a−g. The α,β-unsaturated carboxylic acids **1a**,**b** were prepared by Wittig reaction of the stabilized ylide **9**[24] with ethyl trifluoropyruvate and diethyl ketomalonate, respectively (Scheme 3, eq 1). The product **1a** was obtained as an equimolecular mixture of the *E*/*Z* isomers and used in this form.

Starting from maleic anhydride **10**, we obtained in diastereomerically pure (*E*)-form the fumaric acid monoethyl ester **1c** by ethanolysis in the presence of triethylamine[25] (eq 2), and the aryl ketones **1d**,**e** by Friedel−Crafts acylation of anisole[26] and *p*-fluorobenzene,[27] respectively (eq 3). While 4,4,4-trifluoro-3-trifluoromethyl (Tfm)-crotonic acid **1f** is commercially available, the methyl ketone **1g** was prepared by trapping with the stabilized ylide **9** the pyruvaldehyde produced by in situ oxidation of the hydroxy acetone **11** with MnO_2 in DCM (eq 4).[28]

Reactions with Symmetric Carbodiimides. When symmetric carbodiimides such as DIC (**2a**), DCC (**2b**), 1,3-di-*tert*-butylcarbodiimide (**2c**), and 1,3-*p*-tolylcarbodiimide (**2d**) were reacted with activated α,β-unsaturated carboxylic acids **1a**−**g**, N,N′-disubstituted hydantoins **8a**−**v** were cleanly formed in moderate to good yields (Table 1).

Strongly activated acids **1a** (entries 1−5) and **1b** (entries 6−9) reacted smoothly (less than 5 min) in DCM at 20 °C, producing the corresponding hydantoins **8a**−**h** in good yields. Even sterically congested 1,3-di-*tert*-butylcarbodiimide **2c** gave satisfactory results (entries 3 and 8),[29] while 1,3-*p*-tolylcarbodiimide **2d** reacted sluggishly (entries 4 and 9). Acid **1a** gave rise to low diastereoselection both when reacted as an equimolar mixture of the *E*/*Z* isomers (formation of the two epimeric hydantoins **8a**−**d** in a 1:1 mixture was observed, entries 1−4) and when reacted as pure (*Z*)-isomer isolated by flash chromatography (FC) of the mixture (the epimeric hydantoins **8a** formed in a 2.5:1 mixture, entry 5). The stereochemistry of one of the diastereoisomers **8c** was unambiguously assigned by X-ray analysis (see Supporting Information).

Less activated fumaric acid monoethyl ester **1c** required longer reaction times (DCM, overnight, 20 °C); however, satisfactory results were obtained as well with **2a**,**b** (entries 10 and 11), and even **2d** (entry 13), while sterically congested **2c** reacted sluggishly (entry 12),[30] affording the *N*-acylurea **6k**, arising from O→N acyl migration of the intermediate *O*-acyl isourea, as a major product (30% yield). Under these conditions, less reactive aryl γ-oxo-α,β-unsaturated carboxylic acids **1d**,**e** did not react with carbodiimide **2b** (entries 14 and 21). To increase the reactivity of **1d**, we tried to perform the reaction in the presence of a catalytic amount of a base

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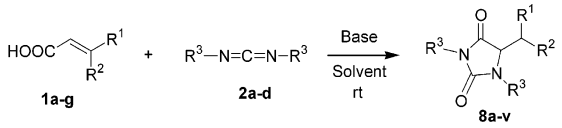
(29) Reaction between **1b** and **2c** (Table 1, entry 8) was performed in an NMR tube: neither ^1H nor ^{13}C NMR spectroscopy allowed us to detect any putative intermediate, as the final hydantoin **8g** formed immediately.

(30) Use of a catalytic base did not improve the outcome of the reactions involving **2c**.

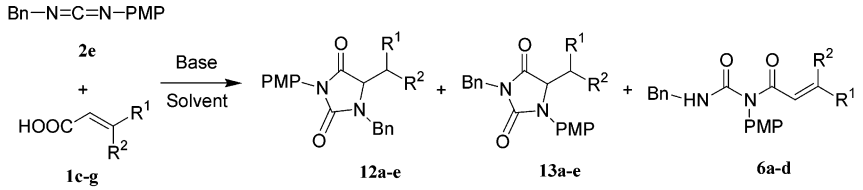
TABLE 1. Synthesis of N,N′-Disubstituted Hydantoins 8a−v



Entry	Acid	Carbodiimide	R^1	R^2	R^3	Base (eq.)	Solvent	Product	Yield (%)
1[a]	**1a**	**2a**	CO_2Et	CF_3	*i*-Pr	None	CH_2Cl_2	**8a**	70[b,d]
2[a]	**1a**	**2b**	CO_2Et	CF_3	*cyclo*-Hexyl	None	CH_2Cl_2	**8b**	88[b,d]
3[a]	**1a**	**2c**	CO_2Et	CF_3	*t*-Bu	None	CH_2Cl_2	**8c**	76[b,d]
4[a]	**1a**	**2d**	CO_2Et	CF_3	*p*-Tol	None	CH_2Cl_2	**8d**	38[b,e]
5	***Z*-1a**	**2a**	CO_2Et	CF_3	*i*-Pr	None	CH_2Cl_2	**8d**	80[c,d]
6	**1b**	**2a**	CO_2Et	CO_2Et	*i*-Pr	None	CH_2Cl_2	**8e**	70[d]
7	**1b**	**2b**	CO_2Et	CO_2Et	*cyclo*-Hexyl	None	CH_2Cl_2	**8f**	60[d]
8	**1b**	**2c**	CO_2Et	CO_2Et	*t*-Bu	None	CH_2Cl_2	**8g**	64[d]
9	**1b**	**2d**	CO_2Et	CO_2Et	*p*-Tol	None	CH_2Cl_2	**8h**	n.r.[e,f]
10	**1c**	**2a**	CO_2Et	H	*i*-Pr	None	CH_2Cl_2	**8i**	67[e]
11	**1c**	**2b**	CO_2Et	H	*cyclo*-Hexyl	None	CH_2Cl_2	**8j**	65[e]
12	**1c**	**2c**	CO_2Et	H	*t*-Bu	None	CH_2Cl_2	**8k**	10[e,g]
13	**1c**	**2d**	CO_2Et	H	*p*-Tol	None	CH_2Cl_2	**8l**	60[e]
14	**1d**	**2b**		H	*cyclo*-Hexyl	None	CH_2Cl_2	**8m**	n.r.[e,f]
15	**1d**	**2b**		H	*cyclo*-Hexyl	DMAP (cat.)	CH_2Cl_2	**8m**	12[e]
16	**1d**	**2b**		H	*cyclo*-Hexyl	DMAP (cat.)	CH_3CN	**8m**	16[e]
17	**1d**	**2a**		H	*i*-Pr	TMP (0.5)	CH_3CN	**8n**	41[e]
18	**1d**	**2b**		H	*cyclo*-Hexyl	TMP (1)	CH_3CN	**8m**	72[e]
19	**1d**	**2a**		H	*i*-Pr	TMP (1)	CH_3CN	**8n**	65[e]
20	**1d**	**2d**		H	*p*-Tol	TMP (1)	CH_3CN	**8o**	65[e]
21	**1e**	**2b**		H	*cyclo*-Hexyl	None	CH_2Cl_2	**8p**	n.r.[e,f]
22	**1e**	**2b**		H	*cyclo*-Hexyl	TMP (1)	CH_3CN	**8p**	40[e]
23	**1e**	**2b**		H	*cyclo*-Hexyl	TMP (1)	DMF	**8p**	65[e]
24	**1e**	**2a**		H	*i*-Pr	TMP (1)	DMF	**8q**	60[e]
25	**1f**	**2b**		H	*cyclo*-Hexyl	TMP (1)	CH_3CN	**8r**	71[e]
26	**1f**	**2d**		H	*p*-Tol	TMP (1)	CH_3CN	**8s**	66[e]
27	**1g**	**2a**	CF_3	CF_3	*i*-Pr	None	CH_2Cl_2	**8t**	50[e]
28	**1g**	**2b**	CF_3	CF_3	*cyclo*-Hexyl	TMP (1)	CH_3CN	**8u**	100[c]
29	**1g**	**2d**	CF_3	CF_3	*p*-Tol	TMP (1)	CH_3CN	**8v**	68[e]

[a] **1a** used in nearly equimolar *E*/*Z* ratio. [b] Equimolar mixture of two diastereomers. [c] Two diastereomers with dr = 2.5/1.0. [d] Time = 5 min. [e] Overnight. [f] No reaction observed. [g] Formation of the corresponding *N*-acylurea was observed.

TABLE 2. Reaction with Strongly Asymmetric *N*-Benzyl-*N'*-*p*-methoxyphenylcarbodiimides 2e



Entry	Acid	R^1	R^2	Base	Solvent	Products	Ratio 12/13/6	Total yield (%)
1[a]	**1c**	COOEt	H	None	DCM	**12a, 13a, 6a**	67/0/33	70
2[a]	**1c**	COOEt	H	TMP[b]	CH_3CN	**12a, 13a, 6a**	50/50/0	68
3[a]	**1d**		H	TMP[b]	DCM	**12b, 13b, 6b**	0/0/100	> 98
4[a]	**1d**		H	TMP[b]	CH_3CN	**12b, 13b, 6b**	25/0/75	86
5[a]	**1d**		H	TMP[b]	DMF	**12b, 13b, 6b**	67/0/33	81
6[a]	**1e**		H	TMP[b]	DMF	**12c, 13c, 6c**	67/0/33	62
7[a]	**1f**		H	TMP[b]	CH_3CN	**12d, 13d, 6d**	0/0/100	68
8[a]	**1f**		H	TMP[b]	DMF	**12d, 13d, 6d**	25/0/75	67
9[a]	**1g**	CF_3	CF_3	TMP[b]	DCM	**12e, 13e, 6e**	100/0/0	67
10[a]	**1g**	CF_3	CF_3	TMP[b]	CH_3CN	**12e, 13e, 6e**	50/50/0	68

[a] Overnight. [b] Performed with 1 equiv.

(DMAP, DCM, overnight, 20 °C) obtaining the formation of the hydantoin **8m** in low yield (entry 15). A slight increase of yield was obtained performing the reaction in CH_3CN instead of DCM (entry 16). An even better yield of the hydantoin **8n** was achieved performing the reaction in CH_3CN with 0.5 equiv of a base (entry 17) such as *sym*-collidine (TMP). Finally, good yields of products **8m**−**o** were achieved using an equimolar amount of base (entries 18−20), even with the less reactive carbodiimide **2d**. In contrast, the *p*-fluoro derivative **1e** gave only a moderate yield of the hydantoin **8p** (entry 22). Since the reaction was apparently strongly dependent on the polarity of the solvent, we tried to increase the reactivity of **1e** performing the reaction in DMF. Indeed, satisfactory results were obtained with carbodiimides **2a**,**b** (entries 23 and 24). Using CH_3CN as a solvent and 1.0 equiv of base, aliphatic 4-oxo-pent-2-enoic acid **1f** showed good reactivity with carbodiimides **2b**,**d** providing hydantoins **8r**,**s**, respectively, in good yields (entries 25 and 26). Finally, despite its two electron-withdrawing groups in the β position, 4,4,4-trifluoro-3-Tfm-crotonic acid **1g** reacted sluggishly with carbodiimide **2a** in the absence of a base (entry 27). However, it showed a good reactivity with carbodiimides **2b**,**d** in CH_3CN in the presence of an equimolar amount of the base, producing hydantoins **8u**,**v** in very good yields (entries 28 and 29).

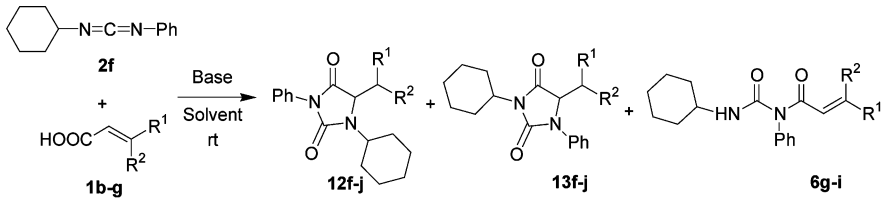
Reactions with Asymmetric Carbodiimides. Next, to expand the scope of the process, we investigated the reaction of carboxylic acids **1b**−**g** with asymmetric carbodiimides **2e**−**h** (Tables 2−5). The latter were prepared by dehydration of asymmetric ureas, which were obtained in turn by reaction of amines with isocyanates, with bromotriphenylphosphorane prepared in situ from bromine and triphenyl phosphine.[31] With the goal of achieving regioselectivity in the key intramolecular aza-Michael step, we chose to use asymmetric carbodiimides having different functionalities at the nitrogen atoms in terms of nucleophilic character and/or steric bulkiness, depending on the R^3 and R^4 appendages.[32]

$$R^3—N=C=N—R^4$$

"strongly asymmetric" carbodiimides: R^3 = alkyl and R^4 = aryl
"weakly asymmetric" carbodiimides: both R^3 and R^4 = alkyl or aryl

For the sake of clarity, carbodiimides having R^3 = alkyl and R^4 = aryl will be dubbed "strongly asymmetric", and

TABLE 3. Reaction with Strongly Asymmetric *N*-Cyclohexyl-*N′*-phenylcarbodiimide 2f



Entry	Acid	R^1	R^2	Base	Solvent	Products	Ratio **12/13/6**	Total yield (%)
1[a]	**1b**	CO_2Et	CO_2Et	None	DCM	**12f, 13f, 6f**	100/0/0	72
2[b]	**1c**	CO_2Et	H	None	DCM	**12g, 13g, 6g**	40/0/60	72
3[b]	**1c**	CO_2Et	H	TMP[c]	CH_3CN	**12g, 13g, 6g**	23/0/67	63
4[b]	**1d**		H	TMP[c]	CH_3CN	**12h, 13h, 6h**	0/0/100	80
5[b]	**1d**		H	TMP[c]	DMF	**12h, 13h, 6h**	21/4/75	85
6[b]	**1e**		H	TMP[c]	DMF	**12i, 13i, 6i**	40/4/56	78
7[b]	**1g**	CF_3	CF_3	TMP[c]	DCM	**12j, 13j, 6j**	100/0/0	83
8[b]	**1g**	CF_3	CF_3	TMP[c]	CH_3CN	**12j, 13j, 6j**	50/50/0	82

[a] Time = 5 min. [b] Overnight. [c] Performed with 1 equiv.

those having both R^3 and R^4 = alkyl or aryl will be dubbed "weakly asymmetric". We first investigated the reactivity of strongly asymmetric *N*-benzyl-*N′*-*p*-methoxyphenyl (PMP) carbodiimide **2e** (Table 2).

In contrast with symmetric carbodiimides (see above), formation of a detectable amount of the *N*-acylurea byproduct **6** was observed in nearly all cases. The reaction between fumaric acid monoethyl ester **1c** and **2e** showed high regioselectivity and scarce chemoselectivity when performed in DCM in the absence of a base. In fact, a ca. 2:1 mixture of hydantoin **12a** and *N*-acylurea **6a** (70% total yield) was obtained (Table 2, entry 1). In contrast, in CH_3CN and in the presence of a base, the reaction was completely chemoselective but not regioselective, producing a 1:1 mixture of the two hydantoins **12a** and **13a** in 68% yield (entry 2). Less reactive aryl and alkyl γ-oxo-α,β-unsaturated carboxylic acids **1d**−**f** reacted smoothly in polar solvents, affording totally regioselective but poorly chemoselective reactions (except **1f** in CH_3CN, which gave exclusively the urea **6d**) and producing mixtures of hydantoins **12b**−**d** and *N*-acylureas **6b**−**d**, respectively, in good total yields (entries 3−8). Finally, highly reactive 4,4,4-trifluoro-3-Tfm-crotonic acid **1g** produced the hydantoin **12e** in good yield, as a unique product, in DCM (entry 9). Formation of an equimolar mixture of the two hydantoins **12e** and **13e** in 68% total yield was achieved performing the reaction in CH_3CN (entry 10). The structure of hydantoin **12e**, and thus the regiochemical course of the reaction, was unambiguously determined by X-ray diffraction analysis (see Supporting Information).

Importantly, *N*-acylurea byproducts **6b**,**d**, whose structure was unambiguously assigned by ^1H NMR analysis, could be converted in good yields into the corresponding hydantoins **12b**,**d** by treatment with NaH in dry DMF (Scheme 4). Clearly, this strongly improves the synthetic methodology, as it permits the recycle of a relevant side-product. It is worth noting that *N*-acylureas **6** are stable compounds that do not convert spontaneously into hydantoins **9**.

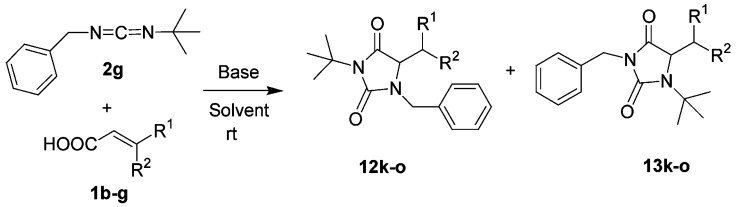
Next, we checked the behavior of more sterically congested strongly asymmetric *N*-cyclohexyl-*N′*-phenylcarbodiimide **2f** (Table 3).

As expected, highly reactive acid **1b** reacted smoothly with **2f**, giving hydantoin **12f** as the only product in very good yield (Table 3, entry 1). The reaction between **2f** and less activated acids **1c**−**e** proved to be less effective in comparison with **2e** probably due to the bulkier character of the *N*-cyclohexyl moiety of **2f** with respect to the *N*-benzyl in **2e**, which slows the intramolecular aza-Michael step. In fact, fumaric acid monoethyl ester **1c** reacted with carbodiimide **2f**, affording *N*-acylurea **6g** as a major product and the hydantoin **12g** as a minor product (entries 2 and 3). Aryl γ-oxo-α,β unsaturated carboxylic acids **1d**,**e**, which were scarcely reactive in DCM, also produced *N*-acylureas **6h**,**i** as major products, even in a very polar solvent such as DMF (entries 4−6).

(31) Palomo, C.; Mestres, R. *Synthesis* **1981**, 373−374.

(32) Examples of regioselective reactions exploiting the reactivity of asymmetric carbodiimides: (a) Larksarp, C.; Alper, H. *J. Org. Chem.* **1998**, *63*, 6229−6233. (b) Heras, M.; Ventura, M.; Linden, A.; Villalgordo, J. M. *Tetrahedron* **2001**, *57*, 4371−4388.

TABLE 4. Reaction with Weakly Asymmetric *N-tert*-Butyl-*N′*-benzylcarbodiimide 2g



Entry	Acid	R^1	R^2	Base	Solvent	Products	Ratio **12**/**13**	Total yield (%)
1[a]	**1b**	CO_2Et	CO_2Et	None	DCM	**12k, 13k**	100/0	65
2[b]	**1c**	CO_2Et	H	None	DCM	**12l, 13l**	100/0	63
3[b]	**1d**		H	TMP[c]	CH_3CN	**12m, 13m**	50/50	86
4[b]	**1d**		H	TMP[c]	DMF	**12m, 13m**	50/50	92
5[b]	**1e**		H	TMP[c]	DMF	**12n, 13n**	50/50	76
6[b]	**1g**	CF_3	CF_3	TMP[c]	DCM	**12o, 13o**	100/0	75
7[b]	**1g**	CF_3	CF_3	TMP[c]	CH_3CN	**12o, 13o**	100/0	77

[a] Time = 5 min. [b] Overnight. [c] Performed with 1 equiv.

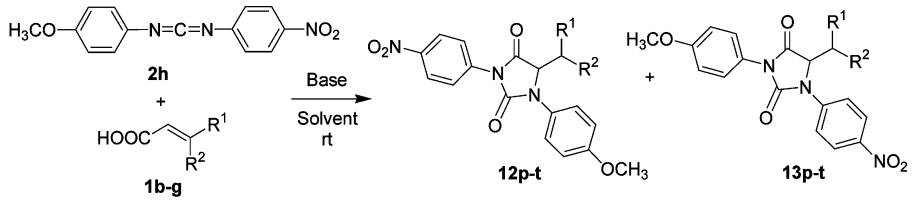
Moreover, in these reactions, together with hydantoins **12h**,**i**, we noticed also the formation of a small amount of the other regioisomeric hydantoins **13h**,**i** derived from intramolecular aza-Michael addition of the less nucleophilic aniline moiety. Also in this case, the *N*-acylurea **6h** could be transformed into the hydantoin **12h** (80%) using the same condition shown above (see Scheme 4). The reaction between 4,4,4-trifluoro-3-Tfm-crotonic acid **1g** and carbodiimide **2f** was chemo- and regiospecific in DCM, giving rise exclusively to the hydantoin **12j** in very good yield (entry 7), whereas the same reaction performed in CH_3CN produced without regioselectivity an equimolar mixture of the two hydantoins **12j** and **13j**.

Next, we investigated the behavior of weakly asymmetric dialkyl carbodiimides. Considering that the key intramolecular N-Michael step was shown to be remarkably sensitive to steric hindrance and hoping to obtain regioselective reactions, we synthesized a model carbodiimide **2g** bearing a tertiary alkyl group (*tert*-butyl) and a primary alkyl group (benzyl); then, we studied its reactivity with acids **1b**−**g** (Table 4). In analogy with symmetric carbodiimides, with **2f** we never detected the formation of *N*-acylurea byproducts. Fumaric acids **1b**,**c** with **2g** in DCM gave totally selective reactions with just the formation of the favorite hydantoins **12k**,**l** produced by the nucleophilic attack of the less hindered benzylamine moiety (entries 1 and 2). Less reactive aryl γ-oxo-α,β unsaturated carboxylic acids **1d**,**e**, which are scarcely reactive in DCM, produced an equimolar mixture of hydantoins **12m**,**n** and **13m**,**n** both in DMF and in less polar CH_3CN (entries 3−5). 4,4,4-Trifluoro-3-Tfm-crotonic acid **1g** gave a completely selective reaction, affording only the hydantoin **12o** both in DCM (entry 6) and in CH_3CN (entry 7). The latter results suggest that, when the difference of nucleophilicity or bulkiness between the two alkylic nitrogen substituents on the carbodiimides is high and the α,β-unsaturated carboxylic acids are highly activated, the solvent has little or no influence on the selectivity.

Finally, we tested the reactivity of weakly asymmetric carbodiimide **2h**, which has two different aromatic substituents (Table 5). In this case, the regioselectivity could arise from the higher electron density, and therefore higher nucleophilicity, on the nitrogen atom of the anisidine moiety with respect to the electron-poor 4-nitro aniline moiety.

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. However, complete chemoselectivity was obtained in all cases, and no formation of *N*-acylurea byproducts was detected. The best regioselectivity was achieved with the most activated acid **1b** in the presence of 1 equiv of base (**12p**:**13p** = 5:1, Table 5, entry 2), while in the absence of base a 3:1 mixture of hydantoins was obtained (entry 1). As in the case of dialkyl carbodiimide **2g**, the regioselectivity of the reaction of **2h** with 4,4,4-trifluoro-3-Tfm-crotonic acid **1g** was not affected by the polarity of the solvent; therefore, the same 4:1 mixture of hydantoins **9t** and **10t** was obtained both in DCM (entry 7) and CH_3CN (entry 8). Finally, with less activated acids **1c**−**e**, no regioselectivity was observed (entries 3−6).

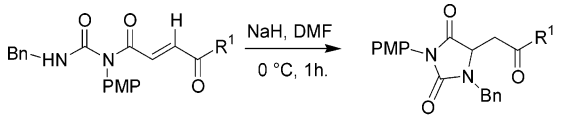
TABLE 5. Reaction with Weakly Asymmetric *N*-*p*-Methoxy-phenyl-*N*′-*p*-nitro-phenylcarbodiimide 2h



Entry	Acid	R^1	R^2	Base	Solvent	Products	Ratio **12**/**13**	Total yield (%)
1[a]	**1b**	CO_2Et	CO_2Et	None	DCM	**12p, 13p**	75/25	65
2[a]	**1b**	CO_2Et	CO_2Et	TMP[d]	DCM	**12p, 13p**	83/17	77
3[b]	**1c**	CO_2Et	H	None	DCM	**12q, 13q**	50/50	66
4[b]	**1c**	CO_2Et	H	TMP[d]	CH_3CN	**12q, 13q**	50/50	n.d.[c]
5[b]	**1d**		H	TMP[d]	CH_3CN	**12r, 13r**	50/50	82
6[b]	**1e**		H	TMP[d]	DMF	**12s, 13s**	50/50	n.d.[c]
7[b]	**1g**	CF_3	CF_3	TMP[d]	DCM	**12t, 13t**	80/20	97
8[b]	**1g**	CF_3	CF_3	TMP[d]	CH_3CN	**12t, 13t**	80/20	91

[a] Time = 5 min. [b] Overnight. [c] Not determined. [d] Performed with 1 equiv.

SCHEME 4. Conversion of *N*-Acylureas 6 into Hydantoins 9



6b,d

R^1 = *p*-Methoxyphenyl **9b** (75%)
R^1 = Me **9d** (75%)

Discussion

The reaction sequence with asymmetric carbodiimides is portrayed in Scheme 5. In the case of symmetric carbodiimides, only two products can be formed, namely, the *N*-acylurea **6** and the hydantoin **8** (see Scheme 2). For asymmetric carbodiimides, the reaction could provide four different products: two regioisomeric hydantoins **12** and **13** and two *N*-acylureas **6** and **6′** (Scheme 5).

The first step involves addition of the carboxylic acid **1** to the carbodiimide **2** to form a reactive intermediate *O*-acyl isourea,[21] existing in two prototropic tautomeric forms **3** and **3′**. An O→N acyl migration can give rise to the corresponding *N*-acylureas **6** and **6′**, which are frequently found byproducts in the condensation reactions of carboxylic acids promoted by carbodiimides. Although little is known on the mechanism of these O→N acyl migrations and on the regioselectivity of the formation of *N*-acylureas from asymmetric carbodiimides, Khorana proposed a rearrangement involving the C=N bond of the intermediate *O*-acyl isoureas.[33] In the case of asymmetric *O*-acyl isoureas, this would lead to **6** from **3** and to **6′** from **3′** (Scheme 5).

(33) Khorana, H. G. *J. Chem. Soc.* **1952**, 2081−2088.

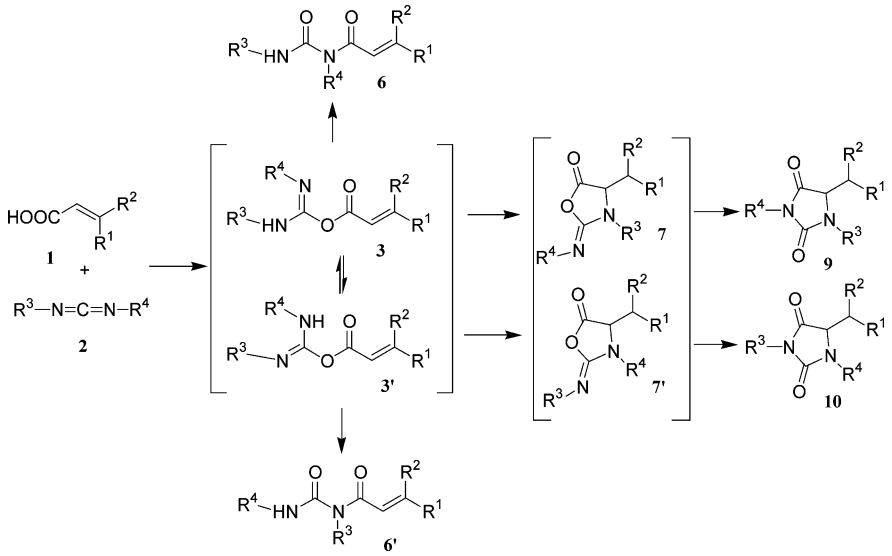
Since the formation of *N*-acylureas **6** and hydantoins **8**, **12**, **13** is under kinetic control, as demonstrated by the fact that these compounds interconvert neither into each other nor into the starting materials **1** and **2**, the mechanism above allows for a valid interpretation of the experimental results.

Concerning the *chemoselectivity* of the process, namely, the competition between formation of *N*-acyl-isoureas **6** and **6′** and hydantoins **12** and **13**, the latter becomes predominant, and even exclusive, with highly activated carboxylic acids. In those cases, the intramolecular aza-Michael reaction leading to the intermediates **7** and **7′** (Scheme 5) appears to be faster than the O→N acyl migrations. On the other hand, the pathway leading to hydantoins is predominant with symmetric ($R^3 = R^4$) or weakly asymmetric (both R^3 and R^4 = alkyl or aryl) carbodiimides (Scheme 6). In fact, *N*-acylurea byproducts were formed only from strongly asymmetric carbodiimides **2e**,**f**, which have one alkyl (R^3) and one aryl group (R^4) as N-substituents.[34] Moreover, only one of the regioisomeric forms, namely, **6**, was observed, whereas **6′** was never detected. This is in line with previous examples of O→N acyl migrations involving asymmetric carbodiimides[35] and could be explained by assuming that in the case of symmetric ($R^3 = R^4$) or weakly asymmetric carbodiimides, the tautomeric forms **3** and **3′** are similarly populated at the equilibrium, and the *O*-acyl isourea

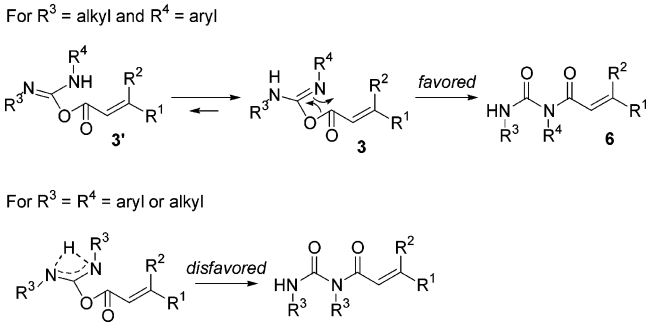
(34) The only exception was a relatively small amount (30%) of *N*-acylurea **6k** formed from one of the reactions involving symmetric *tert*-butyl carbodiimide **2c**. This "abnormal" event could be due to the exceptional steric hindrance of **2c**.

(35) Grünefeld, J.; Zinner, G. *Arch. Pharm. (Weinheim, Ger.)* **1985**, *318*, 1062−1069.

SCHEME 5. Reaction Sequence with Asymmetric Carbodiimides



SCHEME 6. Proposed Mechanism for the Formation of *N*-Acylureas



N−C=N π-system is highly delocalized (Scheme 6). This should make less favorable the rearrangement to **6**, which involves the C=N−R^4 double bond. On the other hand, the observed regioselectivity leading exclusively to the formation of regioisomers **6**, which have R^4 = PMP (*N*-acylureas **6a**−**d**) and R^4 = Ph (**6f**−**i**), should be due to the predominance of regioisomer **3**, which has the C=N bond conjugated with the aromatic π-system.

The *regioselectivity* of the hydantoin formation is regulated by the second reaction pathway involving the intermediate *O*-acyl isoureas **3** and **3′** (Scheme 5), which is an intramolecular aza-Michael reaction leading to the regioisomeric 2-imino-oxazolidin-2-ones **7** and **7′**. Although 2-imino-oxazolidin-2-ones, like **7** and **7′**, have been isolated,[36] it is known that such compounds have a strong proclivity to undergo O→N acyl migration leading to the final hydantoins **12** and **13**, respectively.[21c] Thus, the regioselectivity of the hydantoin formation with asymmetric carbodiimides depends mainly on the difference of nucleophilicity between the two incipient amine moieties N−R^3 and N−R^4 on the carbodiimide: the greater the difference, the higher the regioselectivity. It is therefore not surprising that weakly asymmetric carbodiimides such as **2h** afforded lower regiocontrols in comparison with strongly asymmetric carbodiimides such as **2e**,**f**. In this respect, both electronic and steric differences between R^3 and R^4 appear to be important.

Interestingly, both the chemoselectivity and the regiocontrol of hydantoin formation (but not that of *N*-acylurea formation, which is always 100%) are strongly influenced by experimental factors such as the solvent and the use of a base. Concerning the solvent, the use of more polar solvents (DMF > CH_3CN > DCM) increases the rate of the intramolecular aza-Michael step and thus the chemoselectivity of the process in favor of the hydantoins but in some cases (see, for example, the formation of **12e** and **13e**, Table 2, entries 9 and 10) decreases the regioselectivity of the process. Clearly, this can be interpreted in terms of the well-known accelerating effect of polar solvents on aza-Michael reactions, which generally involve highly polar (and even zwitterionic) intermediates, whereas the O→N acyl migrations do not. On the other hand, the lowering of the kinetic activation energy brought about by the use of polar solvents is expected to be accompanied by a decrease in regioselectivity, since the less nucleophilic N−R functions become more competitive in the aza-Michael attack.

The base has a similar effect, as it is well-known that bases catalyze aza-Michael reactions.[37] Concerning the effect of the base on regioselectivity, the same arguments discussed above for the solvent effect should be applied.

Conclusion

In summary, we have developed a general, straightforward method for the preparation of 1,3,5-trisubstituted hydantoins in good to excellent yields by means of a new domino reaction between carbodiimides and activated α,β-unsaturated carboxylic acids that takes place under very mild conditions. Both the regio- and chemoselectivity of the process are generally very good, although the nature of reactants, as well as reaction parameters such as the solvent and the use (or not) of a base promoter, have strong effects, which have been studied in detail. A large array of structurally diverse 1,3,5-trisubstituted hydantoins can be synthesized through this method, which looks particularly suitable for solid-phase/com-

(36) Brady, W. T.; Owens, R. A. *J. Org. Chem.* **1977**, *42*, 3220−3222.

(37) Molteni, M.; Volonterio, A.; Zanda, M. *Org. Lett.* **2003**, *5*, 3887−3890 and references therein.

binatorial chemistry. Resolution of this issue, as well as the development of a stereoselective version of the domino process, is currently in progress in our laboratory.

Experimental Section

General Methods. Commercially available reagent-grade solvents were employed without purification. Melting points (mp) are uncorrected and were obtained on a capillary apparatus. ^{1}H NMR spectra were run on 250, 400, or 500 MHz spectrometers. Chemical shifts are expressed in parts per million (δ), using tetramethylsilane (TMS) as an internal standard for ^{1}H and ^{13}C nuclei (δ_H and $\delta_C = 0.00$), while C_6F_6 was used as an external standard (δ_F 162.90) for ^{19}F.

General Procedure for the Preparation of 1a. To a stirred solution of ylide **9** (3.0 g, 8.0 mmol) in DCM (40 mL) was added dropwise neat ethyl trifluoropyruvate (1.6 g, 9.5 mmol). The solution was stirred for 90 min, the solvent evaporated in vacuo, and the crude purified through a short silica gel column. The recovered compounds were dissolved in a 20% TFA solution in DCM, and after 2 h the solvent was removed by evaporation. **1a** (7.6 mmol, 95% overall yield) was recovered as a 1:1 mixture of diastereoisomers.

***(E)*-1a:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (br s, 1H), 7.31 (s, 1H), 4.36 (q, J = 7.0 Hz, 2H), 1.36 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.4, 161.0, 135.0 (q, J = 3.4 Hz), 128.5 (q, J = 33.6 Hz), 120.4 (q, J = 274.3 Hz), 63.0, 13.9; ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −66.7 (s, 3F).

***(Z)*-1a:** FTIR (neat) ν 1743, 1724 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (br s, 1H), 6.67 (q, J = 1.3 Hz, 1H), 4.33 (q, J = 7.0 Hz, 2H), 1.30 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.6, 161.2, 135.6 (q, J = 3.1 Hz), 128.9, 120.7 (q, J = 274.3 Hz), 63.1, 13.4; ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −62.9 (s, 3F); EIMS (*m/z*) 212 [M$^+$ (100)].

Synthesis of Hydantoins. Reactions in the Absence of a Base. General Procedure. To a stirred solution of α,β-unsaturated carboxylic acid **1** (1 equiv) in DCM (0.1 M solution) was added 1 equiv of carbodiimide **2**. After total consumption of starting material (TLC monitoring), the organic solvent was evaporated under reduced pressure and the crude purified by flash chromatography.

(*S*,*S*)-(1,3-Diisopropyl-2,5-dioxo-imidazolidin-4-yl)-3,3,3-trifluoro-propionic Acid Ethyl Ester (8a): R_f = 0.30 (hexane/AcOEt = 90:10); FTIR (microscope) ν 1778, 1748, 1703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35−4.18 (m, 4H), 3.92 (dq, J = 9.6 and 1.8 Hz, 1H), 3.65 (septet, J = 7.0 Hz, 1H), 1.42 (d, J = 2.6 Hz, 3H), 1.40 (d, J = 2.6 Hz, 3H), 1.39 (d, J = 6.7 Hz, 3H), 1.29 (d, J = 6.7 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.0, 163.1, 156.3, 123.7 (q, J = 279.3 Hz), 62.4, 57.1, 51.1 (q, J = 27.7 Hz,), 48.4, 44.4, 20.6, 19.6, 19.0, 18.9, 14.1; ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −64.9 (d, J = 9.5 Hz, 3F); EIMS (*m/z*) 338 [M$^+$ (100)], 323 (58), 223 (79).

(*S*,*R*)-(1,3-Diisopropyl-2,5-dioxo-imidazolidin-4-yl)-3,3,3-trifluoro-propionic Acid Ethyl Ester (8a): R_f = 0.27 (hexane/AcOEt = 90:10); FTIR (microscope) ν 1781, 1755, 1713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (s, 1H), 4.35−4.22 (m, 3H), 3.91 (dq, J = 9.0 and 1.6 Hz, 1H), 3.64 (septet, J = 6.7 Hz, 1H), 1.44 (d, J = 6.7 Hz, 3H), 1.39 (d, J = 7.0 Hz, 3H), 1.36 (d, J = 7.0 Hz, 3H), 1.32 (t, J = 7.0 Hz, 3H), 1.26 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.1, 165.1, 156.2, 123.2 (q, J = 283.8 Hz), 63.0, 56.6, 50.4 (q, J = 27.2 Hz), 47.9, 44.3, 20.2, 19.4, 19.1, 19.0, 13.9; ^{19}F NMR (235.4 MHz, $CDCl_3$) δ −63.2 (d, J = 8.6 Hz, 3F); EIMS (*m/z*) 338 [M$^+$ (100)], 323 (64), 223 (80), 83 (78).

Synthesis of Hydantoins. Reactions in the Presence of a Base. General Procedure. To a stirred solution of carbodiimide **2** (1 equiv) in an organic solvent (0.1 M solution) was added 1 equiv of TMP followed by a solution of α,β-unsarurated carboxylic acid **1** (1 equiv) in a minimum amount of the same organic solvent. The resulting solution was stirred overnight. The organic solvent was evaporated under reduced pressure, diluted with AcOEt, and extracted with 1 M HCl aqueous solution. The combined organic layers were dried over anhydrous $NaSO_4$, filtered, and concentrated under vacuum, and the crude was purified by flash chromatography.

Synthesis of Hydantoins Starting from *N*-Acylureas 6. General Procedure. To a stirred solution of *N*-acylurea **6** (1 equiv) in dry DMF (0.1 M solution) was added 1.1 equiv of NaH (60% in weight oil dispersion) at 0 °C under a nitrogen atmosphere. After total consumption of starting material (TLC monitoring), water was added, the organic solvent evaporated under reduced pressure, and the resulting mixture extracted with AcOEt. The combined organic layers were dried over anhydrous $NaSO_4$, filtered, and concentrated under vacuum, and the crude was purified by flash chromatography.

3-Benzyl-1-(4-methoxy-phenyl)-1-[4-(4-methoxy-phenyl)-4-oxo-but-2-enoyl]-urea (6b): R_f = 0.73 (hexane/AcOEt = 50:50); mp 145−147 °C; FTIR (microscope) ν 1724, 1663 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (br t, J = 4.4 Hz, 1H), 7.89 (d, J = 8.8 Hz, 2H), 7.86 (d, J = 15.0 Hz, 1H), 7.40−7.25 (m, 5H), 7.15 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 6.75 (d, J = 15.0 Hz, 1H), 4.56 (d, J = 5.4 Hz, 2H), 3.87 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 187.3, 168.2, 164.2, 160.0, 154.6, 138.1, 135.8, 133.0, 131.2, 130.4, 129.8, 129.7, 128.7, 127.8, 127.5, 115.0, 114.1, 55.5, 55.4, 44.8; EIMS (*m/z*) 444 [M$^+$ (4)], 311 (58), 133 (45), 123 (57), 91 (100).

1-Benzyl-3-(4-methoxy-phenyl)-5-[2-(4-methoxy-phenyl)-2-oxo-ethyl]-imidazolidine-2,4-dione (12b): R_f = 0.59 (hexane/AcOEt = 50:50); mp 107−108 °C; FTIR (microscope) ν 1775, 1727, 1673 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.8 Hz, 2H), 7.30−7.12 (m, 5H), 6.99 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.70 (d, J = 15.3 Hz, 1H), 4.48 (d, J = 15.3 Hz, 1H), 4.46 (dd, J = 5.2 and 3.4 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.51 (dd, J = 17.8 and 3.4 Hz, 1H), 3.33 (dd, J = 17.8 and 5.2 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 193.5, 172.4, 164.0, 159.3, 156.5, 136.2, 130.3, 128.9, 128.8, 128.6, 128.2, 127.8, 127.7, 125.0, 114.4, 113.8, 55.8, 55.5, 45.8, 37.9; EIMS (*m/z*) 444 [M$^+$ (23)], 309 (39), 135 (42), 123 (46), 108 (74), 91 (100).

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Supporting Information Available: Copies of ^{1}H or ^{13}C NMR spectra for compounds **(*Z*)-1a**, **6b**−**d**, **6h**−**i**, **8a**−**g**, **8i**−**u**, **12a**−**m**, **12o**,**p**, and **13n**,**q**−**t**; thermal ellipsoid plot of compounds **8c** and **12e**; characterization data for compounds **6c**,**d**, **6h**−**k**, **8b**−**u**, **12a**,**c**−**t**, **13a**,**e**,**j**,**m**,**n**, and **13p**−**t**; and complete data (excluding structure factor) of the crystal structure in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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