Organic & Biomolecular Chemistry

Cite this: DOI: 10.1039/c2ob26498f

www.rsc.org/obc

PAPER

Regioselective multicomponent sequential synthesis of hydantoins†

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Received 31st July 2012, Accepted 21st September 2012
DOI: 10.1039/c2ob26498f

The development of new practical and green methods for the synthesis of small heterocycles is an attractive area of research due to the well-known potential of heterocyclic small molecule scaffolds in the drug discovery process. Herein we report a one-pot, three-component sequential procedure for the synthesis of diversely 1,3,5- and 1,3,5,5-substituted hydantoins, in high yields and very mild conditions, using readily accessible starting materials such as azides, iso(thio)cyanates and substituted α-halo-acetic carboxylic acids. This methodology is especially convenient for the synthesis of spiro-hydantoins, which are particularly interesting bioactive compounds in medicinal chemistry.

Introduction

The complexity of organic target molecules is constantly increasing and, consequently, novel strategies allowing the efficient formation of new carbon–carbon and carbon–heteroatom bonds between functionalized building blocks are needed. During the past 50 years, extraordinary progress in the discovery of new reagents, reactions, and synthetic strategies has been made.[1] On the other hand, the tools of synthetic organic chemistry are often found inadequate when confronted with the challenge of preparing even modestly elaborate molecules in a practical and concise fashion. A seemingly trivial but rather serious practical limitation is set by the mere number of steps accumulating in linear sequences and by the need for protecting-group strategies. In this respect, step economy is an important factor, since accessibility highly depends on the amount of steps required to reach the desired compounds.[2] Procedures that yield molecules by performing multiple reaction steps in which several bonds are formed without isolation of intermediates are commonly referred to as tandem or domino reactions.[3] Another powerful approach toward this goal is to combine two or more distinct reactions into a single transformation, thereby producing a sequential reaction process.[4] The intrinsic advantage of such a process is twofold: on the one hand it provides a favorable step economy and, on the other hand, it contributes to the implementation of the green chemistry guidelines due to the reduced waste production and increased atom economy. An important subclass of domino reactions are multicomponent reactions (MCRs).[5] Thus, efficiency is also being pursued, when possible, by implementation of classical MCRs in synthetic sequences, as well as by the invention of new protocols. In particular, "one-pot" MC sequential syntheses, in which a number (≥2) of synthetic steps involving three or more reactants are carried out in the same flask without isolation of any intermediate, feature a high degree of reaction mass efficiency and are especially suitable in combinatorial chemistry and diversity-oriented synthesis programs, thus playing a central role in the development of modern synthetic methodology for pharmaceutical and drug discovery research.

Traditionally, methods based on cascade and/or MC reactions have proved quite efficient for the construction of many different types of heterocycles.[6] In fact, many small synthetic organic molecules with biological activity contain heterocyclic rings. Despite the tremendous advancements in the areas of synthetic and combinatorial chemistry, suitably functionalized "privileged" scaffolds are seldom easily or readily accessible. Consequently, the exponentially increased cost of lead generation and optimization has contributed to the introduction of far fewer drugs over the past decade.[7] Thus, new strategies with reduced number of steps and purification procedures, lower costs, and minimized chemical waste are still in high demand. Among the "privileged" heterocyclic scaffolds, hydantoins have been widely used in biological screenings resulting in numerous pharmaceutical applications.[8] In fact, many functionalized hydantoins have been identified as anti-convulsants[9] and antimuscarinics,[10] antiulcers and antiarrythmics,[11] antivirals, antidiabetics,[12] serotonin and fibrinogen receptor antagonists,[13] inhibitors of the glycine binding site of the NMDA receptor,[14] and antagonists of leukocyte cell adhesion acting as allosteric inhibitors of the protein–protein interaction.[15] The observed activities usually do not arise from the heterocycle itself but from the different substituents that have been attached to it. Indeed, by varying the nature of peripheral substituents on this molecular framework, it is often possible to obtain hits across a wide range of biological targets. Moreover, substituted hydantoins are important building

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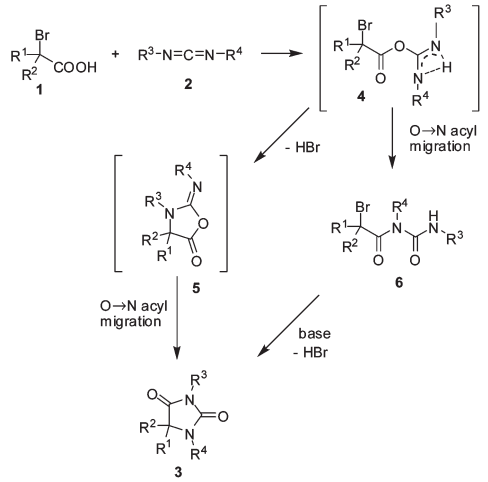
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c2ob26498f

blocks for the synthesis of nonnatural amino acids both in a racemic form by alkaline degradation[16] and in an enantioselective way by enzymatic resolution.[17] For this reason, there is high 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 the reaction of α-amino acids or α-amino nitriles with alkyl, aryl, or chlorosulfonyl isocyanates, respectively, which is a multi-step sequence and requires extended reaction time or high temperatures.[18] 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[19] or *via* Mitsunobu reaction.[20] Various different routes/methods for the synthesis of hydantoins have been recently developed both in solution and in the solid phase to remove the drawbacks associated with the above strategy.[21] However, even if some of these methods allow the synthesis of hydantoins under milder conditions, none of them meet the modern requirements to be "green" and "practical", all of them being multi-step procedures.

Very recently, we have developed an efficient three-component sequential, domino process for the synthesis of libraries of 1,3-disubstituted-5-arylhydantoins with a high degree of diversity starting from simple and easily accessible reactants, such as azides, iso(thio)cyanates and α-bromo-arylacetic acids.[22] In this paper, we provide a full account on the scope and limitations of this new methodology, which has been studied in detail by performing the reaction on many differently substituted α-bromocarboxylic acids. The results reported herein dramatically expand the scope of the process and allow for the preparation of a potentially very large array of structurally diverse, 1,3,5-tri and 1,3,5,5-tetrasubstituted hydantoins, including highly interesting spiro-hydantoin scaffolds,[23] in a mild (room temperature), practical and green fashion.

Results

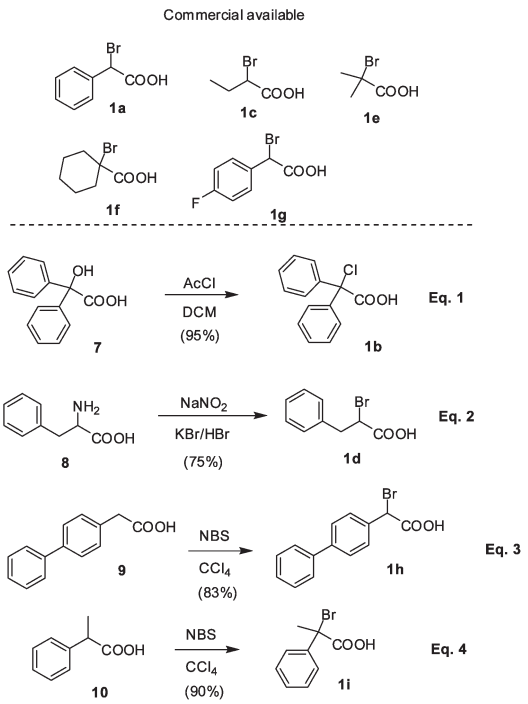
Within an ongoing project aimed at the development of mild domino processes for the synthesis of heterocycles by reacting carbodiimides with suitable carboxylic acids,[24] we envisioned the possibility to synthesize fully substituted hydantoins by using α-bromo-carboxylic acids as starting materials (Scheme 1). Indeed, considering the mechanism of the coupling reaction of carboxylic acids and nucleophiles promoted by carbodiimides,[25] we envisioned that α-bromo-carboxylic acids **1** could react with carbodiimides **2** to form a reactive intermediate *O*-acylisourea **4**, which, in the absence of a nucleophile, could readily cyclize to intermediate **5** through an intramolecular nucleophilic displacement of the halide. The following O → N acyl migration could give rise to the formation of hydantoin **3**. In some cases, the O → N acyl migration could compete with the cyclization, leading to the formation of *N*-acylurea **6** as a by-product or, occasionally, as the main product. However, *N*-acylureas **6** can be convergently transformed into the target hydantoins **3** by *in situ* treatment with a suitable base.



Scheme 1 Synthesis of hydantoins **5**.

Synthesis of the starting materials

When not commercially available (like acids **1a,c,e,f,g**), the starting α-halo-carboxylic acids could be conveniently prepared by two different high yielding strategies, namely α-halogenation of the corresponding acids or esters, or substitution of the amino moiety of the corresponding α-amino acids with bromine *via* a diazonium salt (Scheme 2). The only exception to this is α-chloro-diphenylacetic acid **1b** that was efficiently prepared by treating the corresponding α-hydroxy acid **7** with acetyl chloride in DCM (eqn (1), Scheme 2).[26] Accordingly, α-bromo-3-phenylpropionic acid **1d** was synthesized by treating phenylalanine **8** with sodium nitrite in a HBr/KBr solution (eqn (2), Scheme 2),[27] while bromination of acids **9** and **10** carried out



Scheme 2 Synthesis of the starting α-halo carboxylic acids **1**.

with NBS in CCl_4 gave rise to the formation of the corresponding α-bromo acids **1h,i** in high yields (eqn (3) and (4), Scheme 2).[28]

Reaction with symmetric carbodiimides

In order to assess the suitability of the envisioned process, we started our study with commercially available α-Br-phenylacetic acid **1a**, which features a highly reactive electrophilic atom, namely the benzylic carbon which bears in the α position an excellent leaving group (the halogen atom) and another activating moiety such as the carboxy group. With respect to the carbodiimide component, we chose commercially available symmetric *N*,*N*′-dialkyl carbodiimides, such as DCC and DIC. Accordingly, by reacting **1a** with DCC **2a**, in the presence of 2,4,6-trimethylpyridine (TMP), we obtained the formation of hydantoin **5a** as the only product. The yields of the process were dependent on the solvent: the best result was obtained with apolar DCM (entry 3, Table 1), while lower yields were obtained with more polar solvents such as acetonitrile (entry 1, Table 1) and dioxane (entry 2, Table 1). Similarly, by reacting the same acid **1a** with DIC **2b**, we observed the formation of hydantoin **3b** in moderate yields when the reaction was performed in dioxane and in excellent yields when performed in DCM (entries 4 and 5, respectively, Table 1). As expected, highly reactive α-chloro-diphenylacetic acid **1b** smoothly reacted with DIC **2b** in DCM giving rise to the formation of hydantoin **3c**, although in lower yields (entry 6, Table 1). Less electrophilic α-bromo-butanoic acid **1c** reacted with DCC **2a** producing *N*-acylurea derivative **6a** in modest yields when the reaction was performed in DCM (entry 7, Table 1). By using a more polar solvent, such as dioxane, we increased the overall yields of the process obtaining an almost equimolar mixture of the *N*-acylurea **6a** and the desired hydantoin **3d** (entry 8, Table 1). Rewardingly, the *in situ* addition of a suitable base (aqueous 2 N NaOH solution) triggered the cyclization of **6a** leading to the exclusive formation of hydantoin **3d** in good yields (entry 9, Table 1). Moreover, by carrying out the reaction in highly polar DMF, which facilitates the intramolecular nucleophilic displacement of the halide, we were able to obtain the hydantoin **3d** as the only product without the need for a base (entry 10, Table 1). As expected, also acid **1d** reacted with DCC **2a** and DIC **2b** in DMF producing hydantoins **3e,f**, respectively, in good yield (entries 11 and 12, Table 1). Acid **1e**, bearing the bromine atom on a quaternary carbon, is even less reactive than **1c,d**. Indeed, by reacting **1e** with DCC **2a** in DMF, we obtained the formation of *N*-acylurea **6b** along with the desired hydantoin **3g** in very good yields (entry 13, Table 1). Again, by adding aqueous soda *in situ*, we were able to promote the cyclization pathway with the exclusive formation of hydantoins **3d,e** when acid **1e** was reacted with DCC **2a** and DIC **2b**, respectively (entries 14 and 15, Table 1). Surprisingly, cyclic α-bromo-carboxylic acids such as **1f** were even less reactive than **1e** with respect to the intramolecular nucleophilic substitution. Thus, when **1f** was reacted with DCC **2a** in DMF we obtained the formation of *N*-acylurea derivative **6c** as the sole product in high yields (entry 15, Table 1). The different behaviour in the nucleophilic displacement of the bromine atom was observed also by reacting the intermediate **6c** with an aqueous solution of NaOH which did not trigger the cyclization but led to the formation of a complex mixture of products. However, by using potassium *tert*-butoxide as the base we were able to isolate the desired hydantoin **3i** in good yields (entry 16, Table 1).

It is worth noting that the last process leads to the formation of spiro-hydantoins, a very interesting class of compounds for applications in medicinal chemistry.[23]

Next, we studied the behaviour of less reactive symmetric *N*,*N*′-diaryl carbodiimides (Scheme 3). Since *N*,*N*′-di-*p*-tolyl carbodiimide **2c** is poorly soluble in DCM, we performed the reaction with acid **1a** in dioxane as the solvent, recovering *N*-acylurea derivative **6d** as the only product in high yields (eqn (1), Scheme 3). By adding a 2 N aqueous solution of NaOH *in situ*, we were able to trigger the intramolecular displacement of the bromine atom and to isolate the target hydantoin **3k** very efficiently (eqn (2), Scheme 3). To obtain good results with less reactive acid **1c**, we had to run the reaction in even more polar DMF. Accordingly, when **1c** was reacted with *N*,*N*′-diphenyl carbodiimide **2d** we only recovered *N*-acylurea derivative **6e** (eqn (3), Scheme 3), whereas, by adding potassium *tert*-butoxide at the end of the process, we obtained the clean formation of the corresponding hydantoin in high yields (eqn (4), Scheme 3). Finally, quaternary carboxylic acids **1e,f** reacted smoothly with carbodiimide **2d** giving rise to the formation of the corresponding *N*-acylurea derivatives in high yields (eqn (5) and (6), Scheme 3). However, the *N*-acylurea derived from acid **1e** could be easily and efficiently cyclized to hydantoin **3m** by adding to the reaction mixture a 2 N NaOH aqueous solution (eqn (5), Scheme 3), while we were not able to cyclize *N*-acylurea **6f** either by using sodium hydroxide or potassium *tert*-butoxide, confirming the fact that *N*-acylureas derived from cyclic carboxylic acids are less prone to form the corresponding hydantoins.

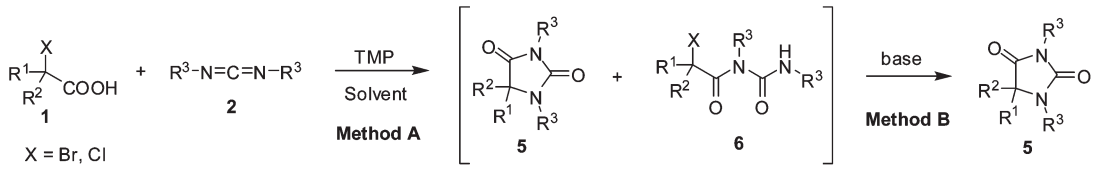
Reaction with asymmetric carbodiimides

In previous work,[24b] we have defined "strongly asymmetric" those carbodiimides that have two very different *N*-substituents in terms of electronic features, such as an aromatic and an alkyl substituent, and "weakly asymmetric" those carbodiimides that have two alkyl substituents at the nitrogen atoms which are very different in terms of steric bulkiness. We have demonstrated that both "strongly" and "weakly asymmetric" carbodiimides react with activated α,β-unsaturated carboxylic acids giving rise to the formation of hydantoins with mostly perfect regioselectivity.[24b]

In order to assess whether the reaction of substituted α-halocarboxylic acids with asymmetric carbodiimides could be used for the regioselective synthesis of fully substituted hydantoins, we decided to use "weakly asymmetric" *N*-benzyl, *N*′-*tert*-butyl carbodiimide **2e** as a model compound (Scheme 4). Gratifyingly, "weakly asymmetric" carbodiimide **2e** reacted smoothly with α-bromo-phenylacetic acid **1a** under the above mentioned conditions, namely TMP and DCM as solvents, giving rise to the formation of hydantoin **3n** as the only regioisomer in very good yields (eqn (1), Scheme 4).

The reaction of the same carbodiimide with less reactive acid **1c** performed in DMF was again completely regioselective even if an almost equimolar mixture of *N*-acylurea **6g** and hydantoin **3o** was formed (eqn (2), Scheme 4). Again, by adding a 2 N

Table 1 Reaction between differently substituted α-haloacetic acids **1** and symmetric *N*,*N*′-dialkylcarbodiimides **2**



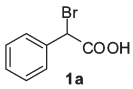
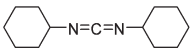
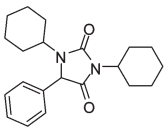
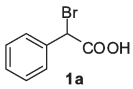
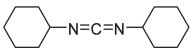
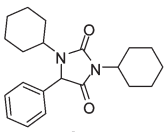
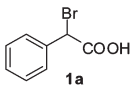
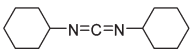
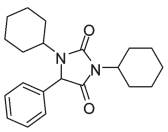
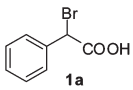
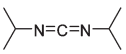
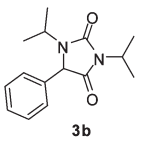
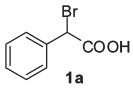
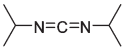
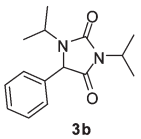
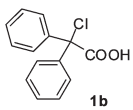
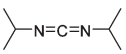
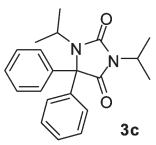
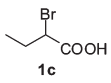
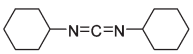
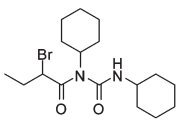
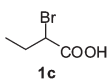
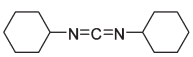
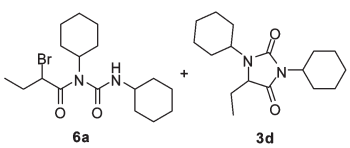
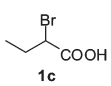
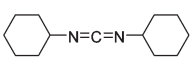
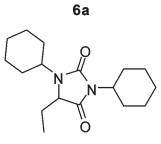
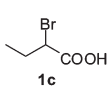
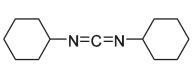
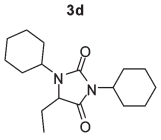
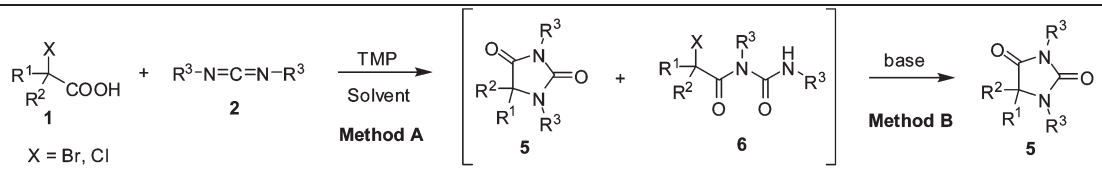
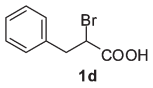
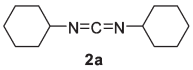
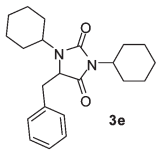
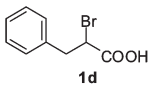
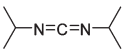
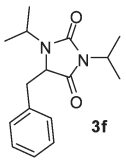
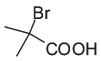
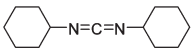
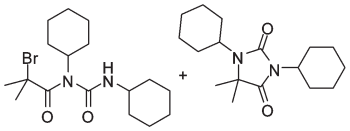
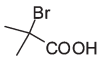
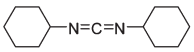
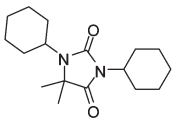
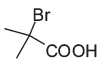
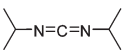
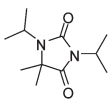
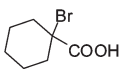
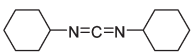
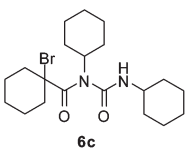
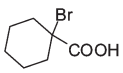
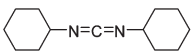
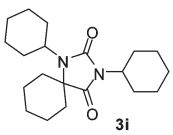
Entry	Acid	Carbodiimide	Solvent	Method	Base	Product	Yield (%)
1	 **1a**	 **2a**	CH_3CN	A	/	 **3a**	33
2	 **1a**	 **2a**	Dioxane	A	/	 **3a**	57
3	 **1a**	 **2a**	DCM	A	/	 **3a**	>98
4	 **1a**	 **2b**	Dioxane	A	/	 **3b**	45
5	 **1a**	 **2b**	DCM	A	/	 **3b**	>98
6	 **1b**	 **2b**	DCM	A	/	 **3c**	68
7	 **1c**	 **2a**	DCM	A	/	 **6a**	46
8	 **1c**	 **2a**	Dioxane	A	/	 **6a** **3d**	35% (**6a**) 44% (**3d**)
9	 **1c**	 **2a**	Dioxane	A + B	NaOH (2 N)	 **3d**	68
10	 **1c**	 **2a**	DMF	A	/	 **3d**	65

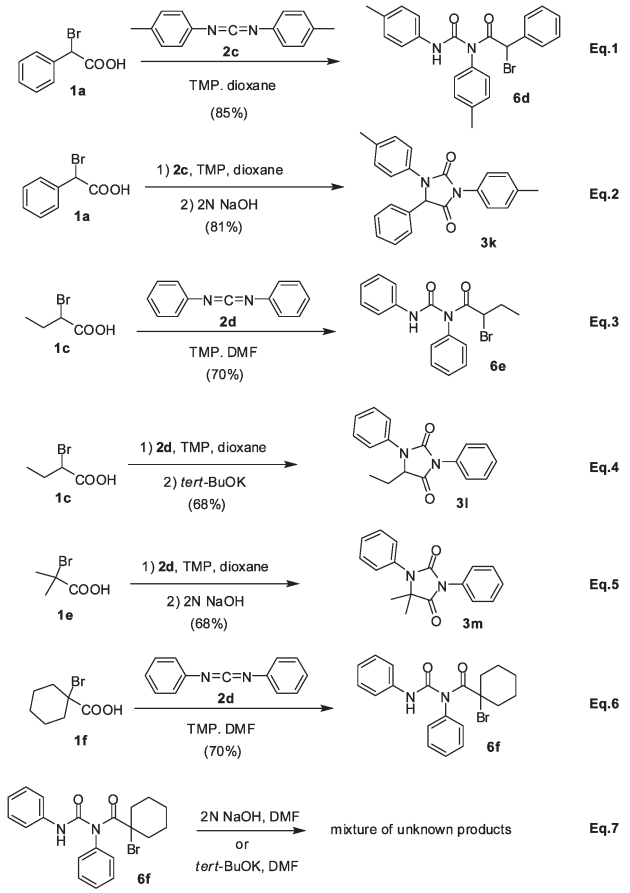
Table 1 *(Contd.)*



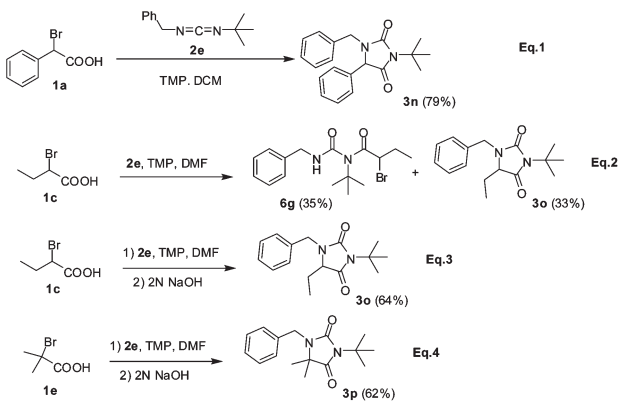
Entry	Acid	Carbodiimide	Solvent	Method	Base	Product	Yield (%)
11	 **1d**	 **2a**	DMF	A	/	 **3e**	71
12	 **1d**	 **2b**	DMF	A	/	 **3f**	65
13	 **1e**	 **2a**	DMF	A	/	 **6b** **3g**	32 (**6b**) 44 (**3g**)
14	 **1e**	 **2a**	DMF	A + B	NaOH (2 N)	 **3g**	66
15	 **1e**	 **2b**	DMF	A + B	NaOH (2 N)	 **3h**	69
16	 **1f**	 **2a**	DMF	A	/	 **6c**	84
17	 **1f**	 **2a**	DMF	A + B	*tert*-BuOK	 **3i**	63

NaOH aqueous solution to the reaction mixture we were able to obtain the exclusive formation of hydantoin **3o**, again as a single regioisomer, in good yields (eqn (3), Scheme 4). Under the same conditions, also unactivated quaternary acid **1e** reacted with **2e** producing hydantoin **3p** as the only regioisomer (eqn (4), Scheme 4).

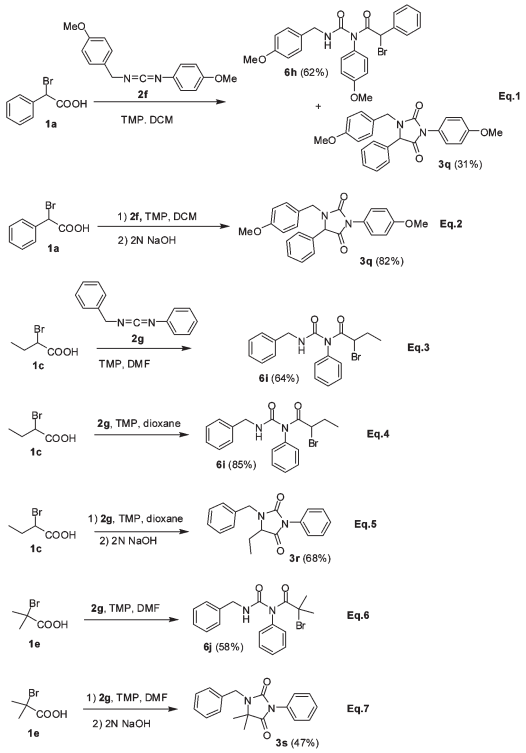
As expected, the process was completely regioselective also with "strongly asymmetric" carbodiimides even if the latter were less reactive than the "weakly asymmetric" ones. In fact, after reacting acid **1a** with *N*-*p*-MeO-benzyl, *N*′-*p*-MeO-phenyl carbodiimide **2f** we recovered an inseparable mixture of *N*-acylurea **6h** and hydantoin **3q** as single regioisomers (eqn (1), Scheme 5). Also in this case, cyclization under Schotten–Bauman conditions led to the regioselective formation of hydantoin **3q** in high yields (eqn (2), Scheme 5). By reacting acid **1c** with *N*-benzyl, *N*′-phenyl carbodiimide **2g**, we obtained the formation of *N*-acylurea **6i** in better yields when the reaction was carried out in dioxane (eqn (4), Scheme 5) as compared to DMF (eqn (3), Scheme 5). Again, triggering the intramolecular nucleophilic displacement of the bromine atom by adding a base (NaOH) to the reaction mixture, we produced hydantoin **3r** in good yields (eqn (5), Scheme 5). Finally, also quaternary carboxylic acid **1e** reacted smoothly with "strongly asymmetric" carbodiimide **2g** giving rise to the formation of *N*-acylurea **6j** (eqn (6), Scheme 5) or hydantoin **3q** when a 2 N NaOH aqueous solution was added at the end of the reaction (eqn (7), Scheme 5).



Scheme 3 Reactions with symmetric *N*,*N*′-diaryl carbodiimides.



Scheme 4 Reactions with "weakly symmetric" *N*-benzyl, *N*′-*tert*-butyl carbodiimide.



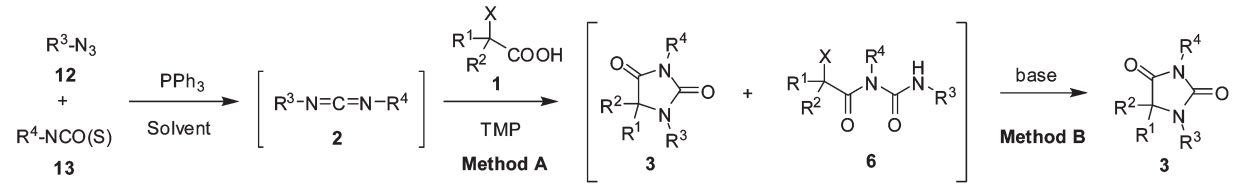
Scheme 5 Reactions with "strongly symmetric" *N*-benzyl, *N*′-phenyl carbodiimide.

MC sequential synthesis of hydantoins 3

With these results in hand, we turned our attention to the possibility of preparing fully substituted hydantoins **3** through an MC sequential process consisting of (1) *in situ* preparation of the reacting carbodiimides **2** through the Staudinger reaction between azides **12** and isocyanates **13**, (2) reaction with the acid **1** to be added to the reaction mixture once the carbodiimide **2** is formed (TLC monitoring), and (3) (when *N*-acylurea intermediates **6** are formed) cyclization triggered by adding a suitable base to the reaction mixture (Table 2).

Therefore, by reacting benzyl azide **12a** with benzyl isocyanate **13a** in the presence of Ph_3P in DCM, we detected the clean formation of carbodiimide **2aa** along with the Ph_3PO by-product (TLC monitoring). Next, by adding to the reacting mixture TMP followed by acids **1a** and **1h**, we observed the formation of hydantoins **3aa,ab**, respectively, in good yields (entries 1 and 2, Table 2). The process worked efficiently also with less reactive acids **1c** and **1f** producing hydantoins **3ac,ad** in acceptable yields (entries 3 and 4, Table 2). In these cases, in order to be able to run the process in an MC sequential fashion, the formation of the carbodiimide **2aa** through the Staudinger reaction was achieved using DMF as a solvent. Moreover, as expected, the reaction between quaternary acid **1f** and *in situ* formed carbodiimide **2aa** led to the formation of the corresponding *N*-acylurea (data not shown) which was cyclized by adding potassium *tert*-butoxide to the reaction mixture. "Weakly asymmetric" carbodiimides reacted straightforwardly also when involved in the MC sequential process. Indeed, the reaction of azide **12b** with commercially available *tert*-butyl isocyanate **13b** cleanly produced carbodiimide **2ab** in DCM which reacted with arylacetic acid **1a** leading to the formation of hydantoin **3ae** as a single regioisomer (entry 5, Table 2). Similarly, carbodiimide **2ac**, obtained from azide **12a** and isocyanate **13b**, reacted with acid **1g** providing hydantoin **3af**, with complete regioselectivity and in good overall yields (entry 6, Table 2). By performing the process in DMF and adding a suitable base when the *N*-acylureas were formed (TLC monitoring), we achieved the regioselective formation of hydantoins **3ag,ah** with acids **1c,f**, respectively

Table 2 Three-component sequential synthesis of 1,3,5- and 1,3,5,5-substituted hydantoins



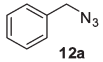
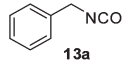
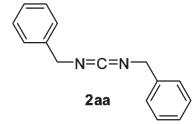
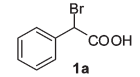
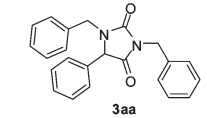
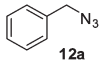
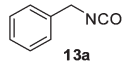
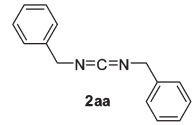
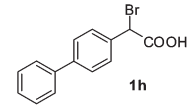
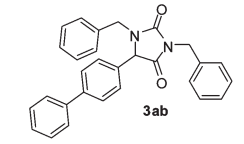
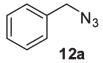
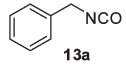
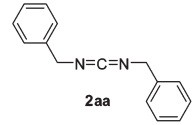
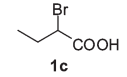
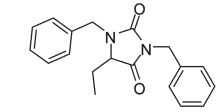
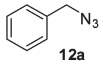
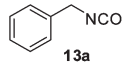
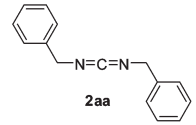
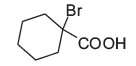
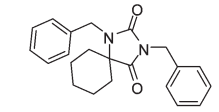
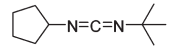
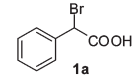
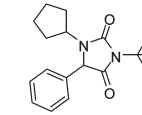
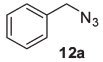
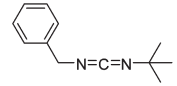
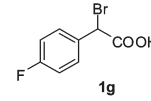
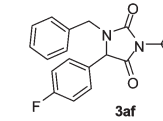
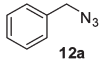
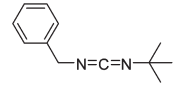
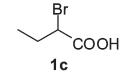
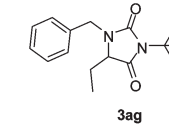
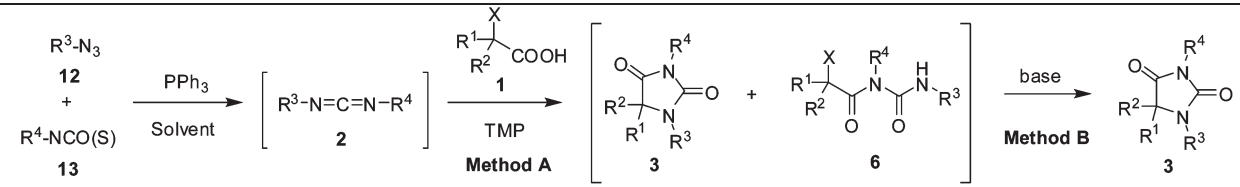
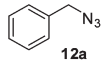
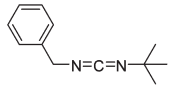
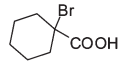
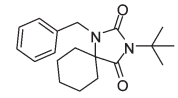
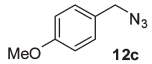
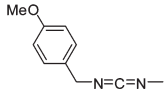
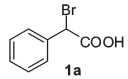
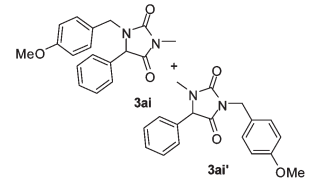
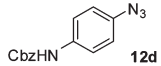
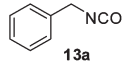
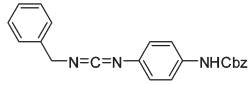
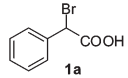
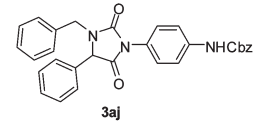
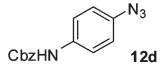
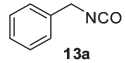
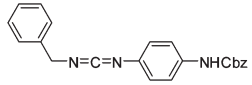
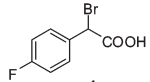
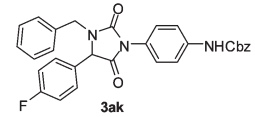
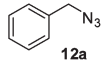
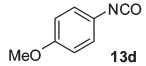
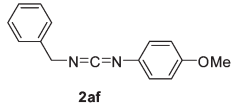
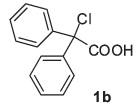
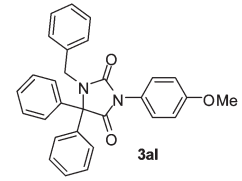
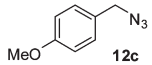
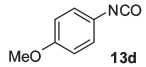
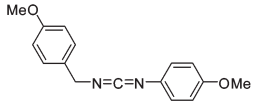
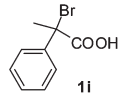
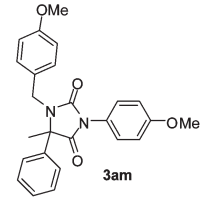
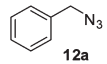
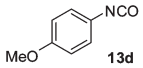
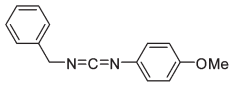
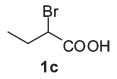
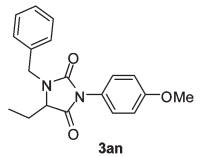
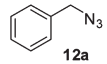
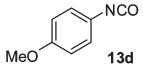
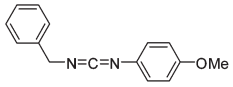
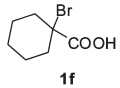
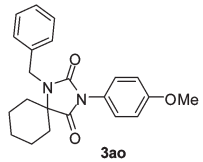
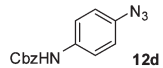
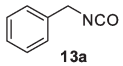
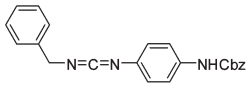
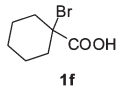
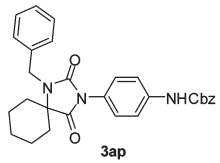
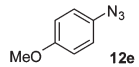
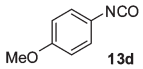
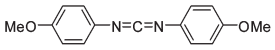
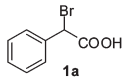
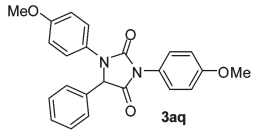
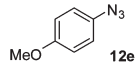
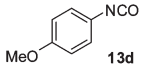
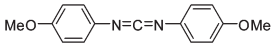
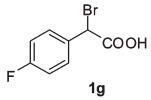
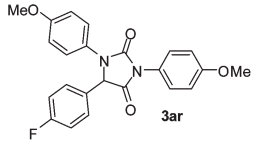
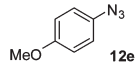
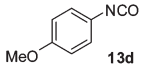
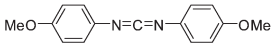
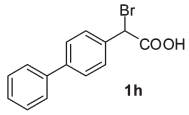
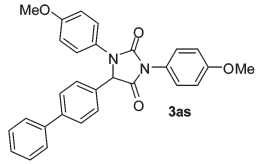
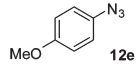
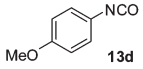
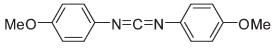
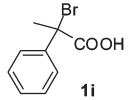
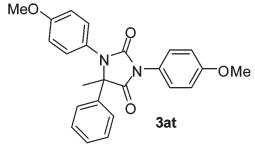
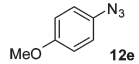
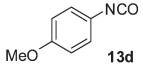
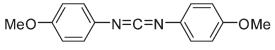
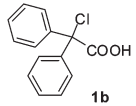
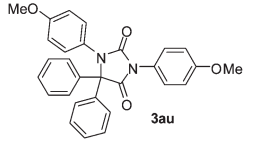
Entry	Azide	Iso(thio)cyanate	Carbodiimide	Acid	Solvent	Method	Base	Product	Yield (%)
1	 12a	 13a	 2aa	 1a	DCM	A	/	 3aa	61
2	 12a	 13a	 2aa	 1h	DCM	A	/	 3ab	63
3	 12a	 13a	 2aa	 1c	DMF	A	/	 3ac	56
4	 12a	 13a	 2aa	 1f	DMF	A + B	*tert*-BuOK	 3ad	51
5	 12b	 13b	 2ab	 1a	DCM	A	/	 3ae	55
6	 12a	 13b	 2ac	 1g	DCM	A	/	 3af	51
7	 12a	 13b	 2ac	 1c	DMF	A + B	2 N NaOH	 3ag	60

Table 2 *(Contd.)*



Entry	Azide	Iso(thio)cyanate	Carbodiimide	Acid	Solvent	Method	Base	Product	Yield (%)
8	 **12a**	 **13b**	 **2ac**	 **1f**	DMF	A + B	*tert*-BuOK	 **3ah**	49
9	 **12c**	–NCS **13c**	 **2ad**	 **1a**	DCM	A	/	 **3ai** **3ai'**	68
10	 **12d**	 **13a**	 **2ae**	 **1a**	DCM	A + B	2 N NaOH	 **3aj**	83
11	 **12d**	 **13a**	 **2ae**	 **1g**	DCM	A + B	2 N NaOH	 **3ak**	90
12	 **12a**	 **13d**	 **2af**	 **1b**	DCM	A	/	 **3al**	69
13	 **12c**	 **13d**	 **2ag**	 **1i**	DCM	A + B	NaOH (2 N)	 **3am**	65

14	 12a	 13d	 2af	 1c	DMF	A + B	NaOH (2 N)	 3an	65
15	 12a	 13d	 2af	 1f	DMF	A + B	*tert*-BuOK	 3ao	72
16	 12d	 13a	 2ae	 1f	DMF	A + B	*tert*-BuOK	 3ap	75
17	 12e	 13d	 2ah	 1a	DCM	A + B	NaOH (2 N)	 3aq	69
18	 12e	 13d	 2ah	 1g	DCM	A + B	NaOH (2 N)	 3ar	72
19	 12e	 13d	 2ah	 1h	DCM	A + B	NaOH (2 N)	 3as	95
20	 12e	 13d	 2ah	 1i	DCM	A + B	NaOH (2 N)	 3at	56
21	 12e	 13d	 2ah	 1b	DCM	A	/	 3au	62

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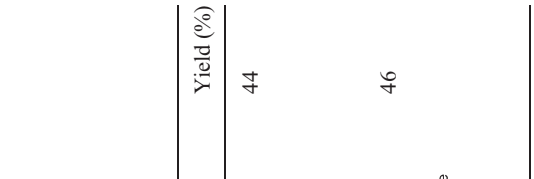
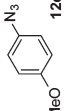
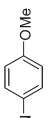
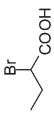
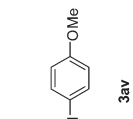


Entry	Azide	Iso(thio)cyanate	Carbodiimide	Acid	Solvent	Method	Base	Product	Yield (%)
22	 **12e**	 **13d**	 **2ah**	 **1c**	DMF	A + B	*tert*-BuOK	 **3av**	44
23	**12e**	**13d**	**2ah**	**1e**	DMF	A + B	NaOH (2 N)	**3aw**	46

(entries 7 and 8, Table 2). As expected, the reactions with "weakly asymmetric" carbodiimide were regioselective only when there is a substantial difference in the steric hindrance of the two carbodiimide *N*-substituents. In fact, when carbodiimide **2ad**, obtained by the Staudinger reaction between *p*-MeO-benzyl azide **12c** and methylisothiocyanate **13c**, was reacted with acid **1a**, we obtained an equimolar mixture of the two regioisomeric hydantoins **3ai,ai′** (entry 9, Table 2).

Thus, we studied the behaviour of "strongly asymmetric" carbodiimides in the MC sequential process. As expected, *in situ* formed carbodiimide **2ae** reacted with highly reactive acids **1a,g** giving rise to the formation of a mixture of the corresponding *N*-acyl-ureas and hydantoins (data not shown). However, by adding a 2 N NaOH aqueous solution once the mixtures were formed, we were able to produce hydantoins **3aj,ak**, respectively, as single regioisomers in excellent yields (entries 10 and 11, Table 2). Even the strongly activated α-chloro-diphenylacetic acid **1b** reacted with *in situ* formed *N*-benzyl, *N′*-*p*-MeO-phenyl carbodiimide **2af** leading to the formation of regioisomeric hydantoin **3al** in DCM and without the need for a base (entry 12, Table 2).

Although less reactive than **1a**, acid **1i** produced regioselectively hydantoin **3am** in good yields upon reaction carried out in DCM with *in situ* formed carbodiimide **2ag**, followed by addition of aqueous NaOH (entry 13, Table 2). As expected, "strongly asymmetric" carbodiimides were effective also with weakly electrophilic α-bromo acids **1c,f** by carrying out the reaction in DMF and triggering the cyclization of the *N*-acylurea intermediates by adding a suitable base to the reaction mixture. Indeed, acid **1c** regioselectively yielded hydantoin **3an** when reacted with *N*-benzyl, *N′*-*p*-MeO-phenyl carbodiimide **2af** and by promoting the nucleophilic displacement of the halide by 2 N NaOH (entry 14, Table 2). The same carbodiimide **2af** as well as *N*-benzyl, *N′*-*p*-NHAc-phenyl carbodiimide **2ae** reacted smoothly with acid **1f** giving rise to the regioselective formation of spiro-hydantoins **3ao,ap**, respectively, in very high yields after promoting the cyclization with potassium *tert*-butoxide (entries 15 and 16, Table 2). Finally, we studied the possibility to synthesize *N*,*N′*-diaryl hydantoins through this MC sequential process. As expected, the Staudinger reaction between *p*-MeO-phenyl azide **12e** and *p*-MeO-phenyl isocyanate **13d** worked very efficiently both in DCM and DMF as solvents, producing carbodiimide **2ah** in almost quantitative yields. Such carbodiimide reacted *in situ* with arylacetic acids **1a,g,h** leading to the formation of hydantoins **3aq-as**, respectively, after cyclization under Schotten–Bauman conditions (entries 17–19, Table 2). Likewise, also acid **1i** was effective in producing hydantoin **3at** in acceptable yields (entry 20, Table 2). Again, more electrophilic diarylacetic acid **1b** yielded hydantoin **3au** with no trace of the intermediate *N*-acylurea (entry 21, Table 2). By shifting the solvent to more polar DMF and triggering the cyclization of the *N*-acylurea intermediates with a suitable base, we could obtain the straightforward synthesis of hydantoins **3av,aw** starting with acids **1c** and **1e**, respectively (entries 22 and 23, Table 2).

Discussion

The reaction between acids **1** and carbodiimides **2** likely takes place by the mechanism depicted in Scheme 1. As already

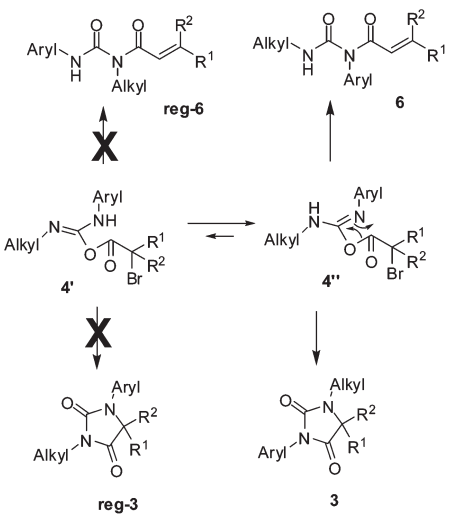
observed in a related process,[24d] the main undesired side reaction that could occur is the decarboxylation of the starting carboxylic acids (leading to a complex mixture of products) that can take place during the proton transfer-nucleophilic step leading to the formation of the highly reactive *O*-acylisourea **3**.[24f] The ease of decarboxylation depends on the structure of the acid, namely the more stabilized the resulting carbanion, the easier the process. Thus, carboxylic acids having one or two phenyl rings in the α-position, like **1a,g,h** and overall **1b**, are more prone to decarboxylation than the corresponding α-alkylacetic acids. However, the decarboxylation pathway could be suppressed or hampered by fine tuning the experimental conditions, mainly by choosing a rather apolar reaction medium. The drawback in using solvents of low polarity is the well-known slowing effect on the nucleophilic intramolecular displacement of the halide which generally involves polar (S_N2 mechanism) or even zwitterionic (S_N1 mechanism) intermediates.

With these considerations in mind, it becomes clear why the reaction between highly basic *N*,*N*′-dialkyl carbodiimides, such as **2a**, and acid **1a** is high yielding only when DCM is used as a solvent, while with more polar dioxane or CH_3CN the yields are significantly lower, probably because the decarboxylation becomes favoured (entries 1–3, Table 1). Indeed, with α-arylacetic acids like **1a**, the intramolecular cyclization step is very fast because the carbon bearing the leaving group is highly electrophilic, being in the α-position to two activating moieties such as a phenyl ring and a carbonyl group, thus the process does not require a highly polar solvent to take place. However, with the exception of highly electrophilic α-chlorodiphenylacetic acid **1b**, when less nucleophilic *N*′-alkyl, *N*′-aryl carbodiimides were reacted with α-arylacetic acids in DCM, a mixture of hydantoin and *N*-acylurea derivatives is always formed, which could be converted to the target hydantoins by using a 2 N NaOH aqueous solution under Schotten–Baumann conditions (Scheme 5 and Table 2). The decarboxylation process depends also on the basicity of the carbodiimide reactants. In fact, poorly basic *N*-*N*′-diarylcarbodiimides, such as **2c**, reacted efficiently with α-bromo-phenylacetic acid **1a** also in more polar solvents, like dioxane, producing *N*-acylurea **6d** in high yields (eqn (1), Scheme 3). The situation is different when α-alkylacetic acids, such as **1c–f**, are used. In this case, the decarboxylation pathway is disfavoured (the resulting carbanion is not stabilized), thus the use of DMF as a solvent is appropriate in order to facilitate the challenging intramolecular nucleophilic displacement of the halide which is not very simple (the reaction between **1c** and DCC **2a** performed in dioxane led to a mixture of *N*-acylurea **6a** and hydantoin **3d**; see entry 8, Table 2). Nevertheless, we did not detect the formation of the *N*-acylurea derivative only when mono-alkylacetic acids **1c,d** reacted with highly nucleophilic *N*,*N*′-dialkyl carbodiimides (entries 9–11, Table 1 and entry 3, Table 2). In all the other cases, *N*-acylurea derivatives were always formed as a mixture with the target hydantoins or as single products (Schemes 3 and 5 and Table 2). Gratifyingly, we were able to promote the cyclization by adding a suitable base to the reaction mixture. In most cases, a 2 N aqueous NaOH solution efficiently triggered the cyclization process leading to the formation of the target hydantoins in fair to high yields. However, when poorly electrophilic α-Br-α-dialkylacetic acids, including cyclic **1f**, were used, the treatment of the corresponding *N*-acylureas with aqueous NaOH did not promote the cyclization, but rather the formation of a mixture of uncharacterized byproducts (data not shown). Probably, this occurs because the cyclization is hampered and the nucleophilic base can promote side reactions. In fact, by using non-nucleophilic potassium *tert*-butoxide we were able to trigger the nucleophilic displacement of the bromine atom in an efficient way (Schemes 3–5 and Table 2), with the exception of *N*-acylureas formed by the reaction of cyclic α-Br-α-*cyclo*-hexylacetic acid **1f** and *N*,*N*′-diaryl carbodiimides (eqn (7), Scheme 3).

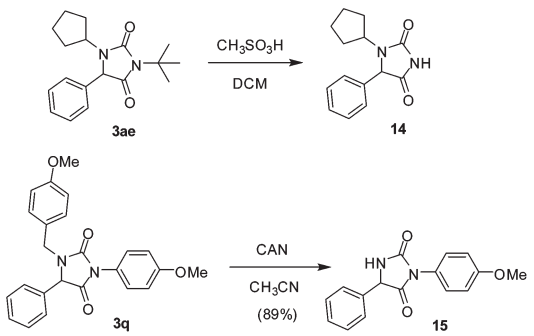
Concerning the reactivity of asymmetric carbodiimides, "strongly asymmetric" *N*-alkyl, *N*′-aryl carbodiimides gave rise to completely regioselective processes in all the cases studied (Scheme 5 and Table 2). Indeed, the regioselectivity achieved in the formation of the hydantoins could be ascribed to the more nucleophilic character of the *N*-alkyl compared to the *N*′-aryl substituent of *O*-acylisourea **4** in the intramolecular nucleophilic substitution step. On the other hand, when *N*-acylureas are formed the regiospecificity likely arises from the predominance of *O*-acylisourea regioisomer **3′′** having the C=N bond conjugated with the aromatic π-system, compared to **3′** (Scheme 6).

Likewise, when the steric hindrance of the two alkylic *N*-substituents of "weakly asymmetric" carbodiimides is very different, the reaction is regioselective producing hydantoins which arise from the nucleophilic attack of the less congested *N*-substituent (Scheme 4 and Table 2), while when the two substituents are very similar, there is virtually no regioselectivity (entry 9, Table 2).

Although with this MC sequential process we can synthesize libraries of diversely *N*,*N*′-disubstituted hydantoins, it is worth noting that, by choosing suitable substituents on the carbodiimide framework, our approach provides access to hydantoins with orthogonal protection on the two nitrogen atoms. For example, we have previously demonstrated that hydantoins bearing a *N*-*tert*-butyl substituent in position 3 can be deprotected by treatment with methansulfonic acid, leading to the formation of 1,5(,5)-substituted hydantoins,[29] such as **14**, while the CAN-mediated oxidative cleavage of the N^1-*p*-MeO-benzyl



Scheme 6 Proposed mechanism for the formation of hydantoins **3′′** and *N*-acylureas **6′′**.



Scheme 7 Chemoselective *N*-deprotection of fully substituted hydantoins.

group of **3q** leads to the formation of 3,5(,5)-substituted hydantoins, such as **15** (Scheme 7).

Conclusions

In summary, we have developed a new, general, straightforward method for the preparation of a large array of diversely 1,3,5- and 1,3,5,5-substituted hydantoins. We exploited a one-pot domino sequential process starting from easily accessible diversely substituted α-halo-acetic acids and carbodiimides. The process works efficiently under mild conditions (room temperature) and is usually totally regioselective when asymmetric carbodiimides are used, although the nature of reactants as well as reaction parameters such as the solvent and the presence (or absence) of a base have strong effects on the final outcome. Moreover, by forming *in situ* the reacting carbodiimide through the Staudinger reaction between azides and iso(thio)cyanates, we have developed a MC sequential process for the preparation of such interesting heterocycles. We have also demonstrated that, by choosing suitable azides or iso(thio)cyanates, we can obtain *N*,*N*′-disubstituted hydantoins which could be chemoselectively deprotected at one of the two nitrogen atoms, thus producing 3,5(,5)- or 1,5(,5)-di(tri)substituted hydantoins.

The operational simplicity, the good chemical yields and the mild conditions combined with favourable atom economy aspects and a small number of synthetic steps render this strategy attractive and promising for the preparation of libraries of differently substituted hydantoins and spiro-hydantoins in a "green" and "practical" fashion. Moreover, this process seems particularly suitable for solid phase/combinatorial chemistry. This latter goal is currently under investigation in our laboratories.

Experimental section

General methods

Commercially available reagent-grade solvents were employed without purification. ^{1}H NMR spectra were acquired on 250, 400 or 500 MHz spectrometers. Chemical shifts are expressed in ppm (δ), using tetramethylsilane (TMS) as an internal standard for ^{1}H and ^{13}C nuclei (δ_H and δ_C = 0.00). MS spectra were recorded with a FT-ICR (Fourier Transform Ion Cyclotron Resonance) instrument, equipped with an ESI source, or a standard MS instrument, equipped with an EI source.

General procedure for the synthesis of hydantoins 3 starting from α-halo acids 1 and carbodiimides 2

To a stirred solution of **1** (1 equiv.) in an appropriate solvent (0.1 M solution), carbodiimide **2** (1.3 equiv.) followed by TMP (1 equiv.) were added at rt and the mixture was stirred overnight. When needed, a 2 N NaOH aqueous solution (10% in volume) or potassium *tert*-butoxide (1.3 equiv.) was added and the mixture stirred at 0 °C until the complete formation of the hydantoin product was detected (TLC monitoring). A 1 N HCl aqueous solution was added until acidic pH, and the resulting mixture extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by flash chromatography.

General procedure for the synthesis of hydantoins 3 under the three-component one-pot sequential process

To a stirred solution of the azide **12** (1.3 equiv.) and isocyanate **13** (1.3 equiv.) in an appropriate solvent (0.1 M) solid PPh_3 (1.3 equiv.) was added and the reaction mixture stirred until the complete formation of the corresponding carbodiimide was detected (TLC monitoring). Next, TMP (1 equiv.) followed by the acid **1** (1 equiv.) were added and the solution stirred overnight. When needed, a 2 N NaOH aqueous solution (10% in volume) or potassium *tert*-butoxide (1.3 equiv.) was added and the mixture stirred at 0 °C until the complete formation of the hydantoin ring was detected (TLC monitoring). A 1 N HCl aqueous solution was added and the resulting mixture extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude was purified by flash chromatography.

1,3-Dicyclohexyl-5-phenylimidazolidine-2,4-dione, 3a. R_f = 0.43 (hexane–AcOEt = 90 : 10); FTIR (nujol) ν 1700, 1684 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 5H), 5.43 (s, 1H), 4.00 (m, 1H), 3.66 (m, 1H), 2.32 (m, 2H), 1.76 (m, 8H), 1.36 (m, 10H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.7, 145.8, 134.5, 129.2, 128.9, 126.1, 79.1, 53.7, 53.1, 34.4, 34.3, 28.5, 28.4, 25.9, 25.8, 25.7, 25.1, 24.7, 24.6; ESI (*m*/*z*) 363.1 [M^+ + Na, (86)], 341.1 [M^+ + 1, (100)]; HRMS calcd for [$C_{21}H_{28}N_2O_2$]: 340.2151, found: 340.2155.

1,3-Diisopropyl-5-phenylimidazolidine-2,4-dione, 3b. R_f = 0.53 (hexane–AcOEt = 80 : 20); FTIR (nujol) ν 1711, 1687 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 5H), 5.44 (s, 1H), 4.41 (septet, J = 7.0 Hz, 1H), 4.00 (septet, J = 6.2 Hz, 1H), 1.45 (d, J = 7.0 Hz, 3H), 1.42 (d, J = 7.0 Hz, 3H), 1.18 (d, J = 6.2 Hz, 3H), 1.16 (d, J = 6.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.6, 145.9, 134.3, 129.2, 128.9, 126.0, 79.1, 46.0, 45.5, 24.33, 24.31, 18.9, 18.8; ESI (*m*/*z*) 283.0 [M^+ + Na, (21)], 261.0 [M^+ + 1, (100)]; HRMS calcd for [$C_{15}H_{20}N_2O_2$]: 260.1525, found: 260.1521.

1,3-Diisopropyl-5,5-diphenylimidazolidine-2,4-dione, 3c. R_f = 0.64 (hexane–AcOEt = 90 : 10); FTIR (nujol) ν 1731,

1687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 4H), 7.37 (m, 6H), 4.42 (septet, J = 6.8 Hz, 1H), 4.10 (septet, J = 6.1 Hz, 1H), 1.43 (d, J = 6.8 Hz, 6H), 1.18 (d, J = 6.1 Hz, 6H); ESI (m/z) 359.1 [M^+ + Na, (65)], 336.1 [M^+ + 1, (100)]; HRMS calcd for [$C_{21}H_{24}N_2O_2$]: 336.1838, found: 336.1842.

1,3-Dicyclohexyl-5-ethylimidazolidine-2,4-dione, 3d. R_f = 0.75 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1714, 1677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.40 (t, J = 5.0 Hz, 1H), 3.84 (m, 1H), 3.46 (m, 1H), 2.16 (m, 2H), 1.84 (m, 1H), 1.63 (m, 10H), 1.18 (m, 7H), 0.84 (t, J = 7.4 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.3, 146.4, 78.7, 53.5, 52.7, 34.3, 34.1, 28.4, 28.3, 25.9, 25.7, 25.1, 24.6, 7.6; ESI (m/z) 293.2 [M^+ + H, (100)], 315.1 [M^+ + Na, (70)]; HRMS calcd for [$C_{17}H_{28}N_2O_2$]: 292.2151, found: 292.2154.

5-Benzyl-1,3-dicyclohexylimidazolidine-2,4-dione, 3e. R_f = 0.61 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1719, 1672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (m, 5H), 4.68 (t, J = 4.5 Hz, 1H), 3.64 (tt, J = 12.4 and 3.8 Hz, 1H), 3.47 (m, 1H), 3.07 (m, 2H), 1.95 (m, 2H), 1.66 (m, 4H), 1.51 (m, 4H), 1.14 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.5, 145.8, 133.9, 130.1, 128.2, 127.2, 77.9, 53.5, 52.5, 37.2, 34.3, 34.1, 28.1, 27.9, 25.9, 25.7, 25.1, 24.6; ESI (m/z) 355.1 [M^+ + H, (100)], 377.1 [M^+ + Na, (85)]; HRMS calcd for [$C_{22}H_{30}N_2O_2$]: 354.2307, found: 354.2311.

5-Benzyl-1,3-diisopropylimidazolidine-2,4-dione, 3f. R_f = 0.34 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1742, 1659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (m, 3H), 7.12 (d, J = 6.5 Hz, 2H), 4.53 (dd, J = 8.7 and 6.4 Hz, 1H), 4.32 (m, 1H), 3.85 (dq, J = 13.2 and 6.6 Hz, 1H), 3.48 (dd, J = 13.8 and 8.7 Hz, 1H), 3.16 (dd, J = 13.8 and 6.3 Hz, 1H), 1.15 (d, J = 6.8 Hz, 6H), 1.09 (d, J = 6.5 Hz, 3H), 1.08 (d, J = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 152.8, 137.0, 129.8, 129.3, 129.1, 129.0, 128.7, 128.6, 127.3, 47.8, 45.5, 43.3, 41.4, 29.7, 22.3, 22.0, 20.5, 20.3; ESI (m/z) 275.1 [M^+ + H, (30)], 297.1 [M^+ + Na, (100)]; HRMS calcd for [$C_{16}H_{22}N_2O_2$]: 274.1681, found: 274.1685.

1,3-Dicyclohexyl-5,5-dimethylimidazolidine-2,4-dione, 3g. R_f = 0.68 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1698, 1656 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.85 (tt, J = 12.3 and 3.8 Hz, 1H), 2.95 (tt, J = 12.1 and 3.7 Hz, 1H), 2.17 (m, 4H), 1.82 (m, 4H), 1.64 (m, 7H), 1.32 (s, 6H), 1.22 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 176.5, 154.1, 61.3, 53.0, 51.1, 32.6, 31.0, 29.4, 26.3, 25.9, 25.5, 25.1, 22.9; ESI (m/z) 315.2 [M^+ + Na, (100)]; HRMS calcd for [$C_{17}H_{28}N_2O_2$]: 292.2151, found: 292.2150.

1,3-Diisopropyl-5,5-dimethylimidazolidine-2,4-dione, 3h. R_f = 0.55 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1709, 1642 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.24 (septet, J = 6.9 Hz, 1H), 3.41 (septet, J = 6.9 Hz, 1H), 1.39 (d, J = 6.9 Hz, 6H), 1.37 (d, J = 6.9 Hz, 6H), 1.30 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 176.4, 153.9, 61.3, 44.7, 43.2, 22.7, 21.0, 19.6; ESI (m/z) 213.3 [M^+ + H, (5)], 235.1 [M^+ + Na, (100)]; HRMS calcd for [$C_{11}H_{20}N_2O_2$]: 212.1525, found: 212.1521.

1,3-Dicyclohexyl-1,3-diazaspiro[4.5]decane-2,4-dione, 3i. R_f = 0.76 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1725, 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.75 (tt, J = 12.3 and 3.8 Hz, 1H), 2.75 (tt, J = 12.1 and 3.9 Hz, 1H), 2.22 (m, 2H), 2.01 (m, 4H), 1.70 (m, 5H), 1.53 (m, 12H), 1.14 (m, 7H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 175.9, 154.2, 62.2, 52.1, 50.7, 31.7, 30.8, 29.3, 26.3, 25.9, 25.1, 25.1, 24.6, 21.2; ESI (m/z) 333.1 [M^+ + H, (25)], 355.1 [M^+ + Na, (100)]; HRMS calcd for [$C_{20}H_{32}N_2O_2$]: 332.2464, found: 332.2463.

5-Phenyl-1,3-di-*p*-tolylimidazolidine-2,4-dione, 3k. R_f = 0.27 (hexane–AcOEt = 80 : 20); FTIR (nujol) ν 1712, 1685 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (m, 7H), 7.35 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 5.58 (s, 3H), 2.40 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 169.1, 153.8, 138.4, 134.7, 133.9, 132.2, 129.7, 129.2, 129.1, 128.9, 126.9, 126.2, 120.8, 64.7, 21.1, 20.7; ESI (m/z) 379.0 [M^+ + Na, (100)], 357.0 [M^+ + 1, (78)]; HRMS calcd for [$C_{23}H_{20}N_2O_2$]: 356.1525, found: 356.1521.

5-Ethyl-1,3-diphenylimidazolidine-2,4-dione, 3l. R_f = 0.35 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1726, 1688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 9H), 7.17 (t, J = 6.9 Hz, 1H), 4.71 (dd, J = 5.4 and 3.0 Hz, 1H), 2.06 (m, 1H), 1.92 (m, 1H), 0.84 (t, J = 7.4 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.9, 153.6, 135.5, 131.5, 129.3, 129.1, 128.3, 126.3, 125.6, 122.1, 60.4, 21.9, 7.0; ESI (m/z) 281.0 [M^+ + H, (5)], 303.0 [M^+ + Na, (100)]; HRMS calcd for [$C_{17}H_{16}N_2O_2$]: 280.1212, found: 280.1209.

5,5-Dimethyl-1,3-diphenylimidazolidine-2,4-dione, 3m. R_f = 0.27 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1709, 1664 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.49 (m, 7H), 7.41 (m, 1H), 7.35 (m, 2H), 1.57 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 175.1, 153.9, 134.0, 131.7, 129.5, 128.9, 128.5, 128.0, 126.1, 63.4, 24.1; ESI (m/z) 281.0 [M^+ + H, (5)], 303.0 [M^+ + Na, (100)]; HRMS calcd for [$C_{17}H_{16}N_2O_2$]: 280.1212, found: 280.1214.

1-Benzyl-3-*tert*-butyl-5-phenyl-imidazolidine-2,4-dione, 3ab. R_f = 0.23 (hexane–AcOEt 90 : 10); FTIR (nujol) ν 1740, 1712, 1531 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 10H), 5.56 (s, 1H), 4.70 (m, 2H), 1.36 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 168.3, 160.6, 129.8, 129.6, 129.1, 128.9, 128.7, 128.5, 128.2, 127.9, 127.3, 126.0, 125.9, 125.9, 80.3, 53.1, 44.0, 27.8; ESI (m/z) 345.0 [M^+ + Na, (100)], 323.1 [M^+ + 1, (90)]; HRMS calcd for [$C_{20}H_{22}N_2O_2$]: 322.1681, found: 322.1684.

1-Benzyl-3-*tert*-butyl-5-ethylimidazolidine-2,4-dione, 3o. R_f = 0.65 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1712, 1629 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 2H), 7.22 (m, 3H), 4.56 (d, J = 0.9 Hz, 2H), 4.54 (dd, J = 6.0 and 4.6 Hz, 1H), 1.90 (m, 1H), 1.73 (m, 1H), 1.21 (s, 9H), 0.82 (t, J = 7.4 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.7, 144.6, 136.3, 129.0, 128.3, 127.7, 80.0, 52.5, 43.5, 30.4, 24.7, 8.0; ESI (m/z) 275.0 [M^+ + H, (80)], 297.0 [M^+ + Na, (100)]; HRMS calcd for [$C_{16}H_{22}N_2O_2$]: 274.1681, found: 274.1679.

1-(4-Methoxybenzyl)-3-(4-methoxyphenyl)-5-phenylimidazolidine-2,4-dione, 3q. R_f = 0.31 (hexane–AcOEt = 70 : 30); FTIR (nujol) ν 1700, 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 5H), 7.38 (d, J = 9.0 Hz, 2H), 7.29 (d, J = 9.0 Hz, 2H), 6.98 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.77 (s, 1H), 4.63 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100.6 MHz,

$CDCl_3$) δ 170.0, 159.4, 158.4, 148.9, 133.4, 132.5, 129.4, 128.9, 128.6, 127.9, 127.0, 126.0, 114.4, 113.7, 80.1, 55.4, 55.2, 48.7; ESI (*m*/*z*) 425.1 [M^+ + Na, (34)], 403.1 [M^+ + 1, (100)]; HRMS calcd for [$C_{24}H_{22}N_2O_4$]: 402.1580, found: 402.1582.

1-Benzyl-5-ethyl-3-phenylimidazolidine-2,4-dione, 3r. R_f = 0.38 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1715, 1624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 6H), 7.31 (m, 3H), 7.20 (t, J = 7.0 Hz, 1H), 4.75 (s, 2H), 4.61 (dd, J = 5.5 and 3.0 Hz, 1H), 2.02 (m, 1H), 1.89 (m, 1H), 0.73 (t, J = 7.4 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.7, 155.9, 135.6, 131.9, 129.2, 129.0, 128.7, 128.6, 128.3, 128.2, 128.0, 126.0, 121.7, 59.1, 44.8, 21.5, 7.1; ESI (*m*/*z*) 317.1 [M^+ + Na, (100)]; HRMS calcd for [$C_{18}H_{18}N_2O_2$]: 294.1368, found: 294.1364.

1-Benzyl-5,5-dimethyl-3-phenylimidazolidine-2,4-dione, 3s. R_f = 0.40 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1709, 1645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 4H), 7.26 (m, 4H), 7.17 (d, J = 8.2 Hz, 2H), 4.68 (s, 2H), 1.35 (s, 6H); ^1H NMR (101 MHz, $CDCl_3$) δ 176.0, 136.3, 129.4, 128.7, 128.5, 128.2, 127.8, 63.8, 42.6, 23.8; ESI (*m*/*z*) 295.1 [M^+ + H, (5)], 317.1 [M^+ + Na, (100)]; HRMS calcd for [$C_{18}H_{18}N_2O_2$]: 294.1368, found: 294.1366.

1,3-Dibenzyl-5-phenylimidazolidine-2,4-dione, 3aa. R_f = 0.37 (hexane–AcOEt = 80 : 20); FTIR (nujol) ν 1701, 1690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (m, 2H), 7.34 (m, 13H), 5.63 (s, 1H), 4.84 (d, J = 14.4 Hz, 1H), 4.79 (d, J = 14.4 Hz, 1H), 4.66 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.8, 148.7, 140.9, 136.1, 133.8, 129.8, 129.3, 129.2, 128.9, 128.6, 128.3, 127.7, 126.9, 126.5, 80.7, 49.4, 44.3; ESI (*m*/*z*) 379.0 [M^+ + Na, (100)], 357.1 [M^+ + 1, (31)]; HRMS calcd for [$C_{23}H_{20}N_2O_2$]: 356.1525, found: 356.1525.

1,3-Dibenzyl-5-biphenyl-4-yl-imidazolidine-2,4-dione, 3ab. R_f = 0.33 (hexane–AcOEt 80 : 20); FTIR (nujol) ν 1705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (m, 5H), 7.36 (m, 15H), 5.68 (s, 1H), 4.85 (d, J = 14.6 Hz, 1H), 4.80 (d, J = 14.6 Hz, 1H), 4.66 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.4, 158.7, 129.3, 128.9, 128.8, 128.7, 128.6, 128.3, 128.0, 127.7, 127.6, 127.3, 127.2, 126.6, 126.5, 125.9, 80.2, 49.0, 44.0; ESI (*m*/*z*) 455.1 [M^+ + Na, (39)], 433.1 [M^+ + 1, (100)]; HRMS calcd for [$C_{29}H_{24}N_2O_2$]: 432.1838, found: 432.1840.

1,3-Dibenzyl-5-ethylimidazolidine-2,4-dione, 3ac. R_f = 0.56 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1722, 1687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.25 (d, J = 4.5 Hz, 7H), 7.17 (m, 1H), 4.71 (d, J = 1.3 Hz, 2H), 4.62 (dd, J = 6.1, 4.7 Hz, 1H), 4.52 (s, 2H), 1.96 (m, 1H), 1.79 (m, 1H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 149.0, 140.7, 135.9, 128.8, 128.5, 128.2, 127.9, 127.2, 126.4, 80.4, 48.8, 43.6, 24.7, 8.1; ESI (*m*/*z*) 309.0 [M^+ + H, (100)], 331.0 [M^+ + Na, (100)]; HRMS calcd for [$C_{19}H_{20}N_2O_2$]: 308.1525, found: 308.1527.

1,3-Dibenzyl-1,3-diazaspiro[4.5]decane-2,4-dione, 3ad. R_f = 0.36 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1709, 1685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 2H), 7.22 (m, 8H), 4.62 (s, 2H), 4.45 (s, 2H), 1.94 (m, 2H), 1.65 (m, 1H), 1.51 (m, 6H), 1.00 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 175.5, 156.0, 138.2, 136.5, 128.7, 128.6, 128.3, 127.7, 127.4, 127.4, 63.5, 42.4, 42.1, 32.4, 24.5, 21.3; ESI (*m*/*z*) 349.1 [M^+ + H, (85)], 371.0 [M^+ + Na, (100)]; HRMS calcd for [$C_{22}H_{24}N_2O_2$]: 348.1838, found: 348.1841.

3-*tert*-Butyl-1-cyclopentyl-5-phenylimidazolidine-2,4-dione, 3ae. R_f = 0.31 (hex–AcOEt = 70 : 30); FTIR (nujol) ν 1689, 1676 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H), 4.76 (s, 1H), 4.07 (quintet, J = 8.0 Hz, 1H), 1.86–1.26 (m, 8H), 1.61 (s, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 136.3, 129.4, 129.2, 128.6, 127.3, 126.8, 63.4, 55.5, 30.5, 29.2, 29.0, 28.8, 23.9, 23.7; ESI (*m*/*z*) 323.1 [M^+ + Na, (21)], 300.1 [M^+, (100)]; HRMS calcd for [$C_{18}H_{24}N_2O_2$]: 300.1838, found: 300.1835.

1-Benzyl-3-*tert*-butyl-5-(4-fluoro-phenyl)-imidazolidine-2,4-dione, 3af. R_f = 0.25 (hexane–AcOEt 90 : 10); FTIR (nujol) ν 1711, 1604, 1509 cm^{-1}; FTIR (nujol) ν 1712, 1658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 9H), 5.53 (s, 1H), 4.70 (d, J = 12.9 Hz, 1H), 4.66 (d, J = 12.9 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.8, 163.1 (d, J = 248.3 Hz), 136.0, 131.6, 131.0, 130.5, 129.1, 128.5, 128.4, 127.9, 127.8, 115.9 (d, J = 22.0 Hz), 79.5, 62.0, 44.0, 30.6, 28.2, 28.0; ^{19}F-NMR (470.6 MHz) δ −112.1 (m, 1F); ESI (*m*/*z*) 363.0 [M^+ + Na, (100)], 341.1 [M^+ + 1, (77)]; HRMS calcd for [$C_{20}H_{21}FN_2O_2$]: 340.1587, found: 340.1584.

1-Benzyl-3-*tert*-butyl-5-ethylimidazolidine-2,4-dione, 3ag. R_f = 0.65 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1709, 1617 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 2H), 7.22 (m, 3H), 4.56 (d, J = 0.9 Hz, 2H), 4.54 (dd, J = 6.0 and 4.6 Hz, 1H), 1.90 (m, 1H), 1.73 (m, 1H), 1.21 (s, 9H), 0.82 (t, J = 7.4 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.7, 144.6, 136.3, 129.0, 128.3, 127.7, 80.0, 52.5, 43.5, 30.4, 24.7, 8.0; ESI (*m*/*z*) 275.0 [M^+ + H, (80)], 297.0 [M^+ + Na, (100)]; HRMS calcd for [$C_{16}H_{22}N_2O_2$]: 274.1681, found: 274.1680.

1-Benzyl-3-*tert*-butyl-1,3-diazaspiro[4.5]decane-2,4-dione, 3ah. R_f = 0.85 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1712, 1619 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 2H), 7.18 (m, 3H), 4.40 (s, 2H), 1.92 (m, 2H), 1.61 (d, J = 13.4 Hz, 1H), 1.56 (s, 9H), 1.47 (m, 6H), 1.01 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 176.9, 156.8, 138.5, 128.6, 127.2, 127.1, 61.4, 57.5, 42.1, 32.5, 28.8, 24.6, 21.3; ESI (*m*/*z*) 315.1 [M^+ + H, (15)], 337.1 [M^+ + Na, (100)]; HRMS calcd for [$C_{19}H_{26}N_2O_2$]: 314.1994, found: 314.1997.

1-(4-Methoxybenzyl)-3-methyl-5-phenylimidazolidine-2,4-dione, 3ai. R_f = 0.13 (hexane–AcOEt = 80 : 20); FTIR (nujol) ν 1704, 1691 cm^{-1}; FTIR (nujol) ν 1706, 1665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 5H), 7.31 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.63 (s, 1H), 4.59 (s, 2H), 3.80 (s, 3H), 3.13 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.6, 158.6, 149.3, 132.6, 129.4, 129.3, 128.9, 128.8, 126.0, 113.9, 80.5, 55.3, 48.6, 26.6; ESI (*m*/*z*) 311.2 [M^+ + 1, (100)]; HRMS calcd for [$C_{18}H_{18}N_2O_3$]: 310.1317, found: 310.1319.

3-(4-Methoxybenzyl)-1-methyl-5-phenylimidazolidine-2,4-dione, 3ai′. R_f = 0.24 (hexane–AcOEt = 80 : 20); FTIR (nujol) ν 1709, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 7H), 6.84 (d, J = 8.8 Hz, 2H), 5.57 (s, 1H), 4.71 (d, J = 14.1 Hz, 1H), 4.65 (d, J = 14.1 Hz, 1H), 3.87 (s, 3H), 3.1 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.5, 159.4, 148.7, 133.6, 130.1,

129.4, 128.9, 128.0, 126.2, 114.0, 80.1, 55.2, 43.3, 32.4; ESI (*m*/*z*) 333.1 [M^+ + Na, (44)], 311.1 [M^+ + 1, (100)]; HRMS calcd for [$C_{18}H_{18}N_2O_3$]: 310.1317, found: 310.1315.

[4-(3-Benzyl-2,5-dioxo-4-phenyl-imidazolidin-1-yl)-phenyl]-carbamic acid benzyl ester, 3aj. R_f = 0.27 (hexane–AcOEt 70 : 30); FTIR (nujol) *ν* 1709.40, 1519; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.32 (m, 19H), 6.83 (s, 1H), 5.68 (s, 1H), 5.12 (s, 2H), 4.60 (s, 2H); ^{13}C NMR (62.3 MHz, $CDCl_3$) *δ* 170.2, 169.9, 155.6, 153.1, 148.8, 140.1, 138.6, 138.1, 137.8, 135.9, 135.1, 133.2, 132.4, 129.8, 129.9, 129.3, 129.1, 129.0, 128.9, 128.8, 128.6, 128.3, 128.2, 127.8, 127.6, 127.4, 127.2, 126.8, 126.6, 126.3, 126.0, 121.5, 120.9, 118.9, 80.1, 79.9, 67.0, 62.9, 49.3, 44.8, 29.6; ESI (*m*/*z*) 514.1 [M^+ + Na, (100)], 492.1 [M^+ + 1, (25)]; ESI (*m*/*z*) 333.1 [M^+ + Na, (44)], 311.1 [M^+ + 1, (100)]; HRMS calcd for [$C_{30}H_{25}N_3O_4$]: 491.1845, found: 491.1849.

{4-[3-Benzyl-4-(4-fluoro-phenyl)-2,5-dioxo-imidazolidin-1-yl]-phenyl}-carbamic acid benzyl ester, 3ak. R_f = 0.30 (hexane–AcOEt 70 : 30); FTIR (nujol) *ν* 1704, 1516; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.35 (m, 16H), 7.11 (m, 2H), 7.03 (s, 1H), 5.72 (s, 1H), 5.19 (s, 2H), 4.67 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 169.7, 163.5 (d, *J* = 249.2 Hz), 153.1, 140.0, 138.1, 135.9, 128.6, 128.3, 128.2, 127.9 (d, *J* = 8.5 Hz), 127.4, 127.2, 126.6, 118.9, 116.1 (d, *J* = 22.0 Hz), 79.4, 67.1, 49.3; ^{19}F NMR (470.6 MHz) *δ* −112.5 (m, 1F); ESI (*m*/*z*) 532.0 [M^+ + Na, (100)], 510.0 [M^+ + 1, (22)]; HRMS calcd for [$C_{30}H_{24}FN_3O_4$]: 509.1751, found: 509.1748.

1-Benzyl-3-(4-methoxy-phenyl)-5,5-diphenyl-imidazolidine-2,4-dione, 3al. R_f = 0.40 (hexane–AcOEt 80 : 20); FTIR (nujol) *ν* 1709, 1514 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.55 (m, 4H), 7.36 (m, 12H), 7.26 (m, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 4.78 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 171.3, 159.9, 148.5, 140.9, 138.3, 129.3, 129.1, 128.7, 128.4, 127.8, 126.9, 126.7, 125.3, 88.1, 55.9, 50.0; ESI (*m*/*z*) 471.0 [M^+ + Na, (100)], 449.1 [M^+ + 1, (50)]; HRMS calcd for [$C_{29}H_{24}N_2O_3$]: 448.1787, found: 448.1786.

1-(4-Methoxy-benzyl)-3-(4-methoxy-phenyl)-5-methyl-5-phenyl-imidazolidine-2,4-dione, 3am. R_f = 0.30 (hexane–AcOEt 80 : 20); FTIR (nujol) *ν* 1706, 1611, 1514 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.55 (d, *J* = 8.5 Hz, 2H), 7.37 (m, 5H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 4.66 (s, 2H), 3.81 (s, 6H), 1.97 (s, 3H); ^{13}C NMR (62.3 MHz, $CDCl_3$) *δ* 172.8, 159.3, 158.4, 148.1, 138.2, 132.7, 128.7, 128.5, 127.8, 124.5, 114.3, 113.7, 84.7, 55.4, 55.2, 48.8, 25.5; ESI (*m*/*z*) 439.0 [M^+ + Na, (100)]; HRMS calcd for [$C_{25}H_{24}N_2O_4$]: 416.1736, found: 416.1736.

1-Benzyl-5-ethyl-3-(4-methoxyphenyl)imidazolidine-2,4-dione, 3an. R_f = 0.43 (hex–AcOEt = 80 : 20); FTIR (nujol) *ν* 1709, 1611 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.39 (m, 3H), 7.21 (m, 4H), 6.80 (d, *J* = 8.4 Hz, 2H), 4.36 (s, 2H), 3.88 (t, *J* = 7.2 Hz, 1H), 3.73 (s, 3H), 2.03 (m, 1H), 1.84 (m, 1H), 0.82 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) *δ* 172.6, 159.1, 154.2, 137.4, 129.9, 129.6, 129.3, 129.2, 129.1, 114.1, 55.3, 47.2, 44.3, 28.1, 11.9; ESI (*m*/*z*) 324.3 [M^+ + H, (100)]; HRMS calcd for [$C_{19}H_{20}N_2O_3$]: 324.1474, found: 324.1471.

1-Benzyl-3-(4-methoxyphenyl)-1,3-diazaspiro[4.5]decane-2,4-dione, 3ao. R_f = 0.26 (hex–AcOEt = 80 : 20); FTIR (nujol) *ν* 1696, 1632 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.33 (m, 5H), 7.09 (dd, *J* = 7.7, 1.5 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 4.59 (s, 2H), 3.72 (s, 3H), 2.00 (m, 2H), 1.79 (d, *J* = 13.9 Hz, 2H), 1.54 (m, 5H), 0.90 (qt, *J* = 12.6, 3.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 175.2, 159.2, 155.2, 133.7, 130.6, 130.0, 129.3, 128.8, 128.7, 114.0, 64.6, 55.2, 41.6, 33.0, 24.3, 21.4; ESI (*m*/*z*) 364.2 [M^+ + H, (100)]; HRMS calcd for [$C_{22}H_{24}N_2O_3$]: 364.1787, found: 364.1788.

Benzyl 4-(1-benzyl-2,4-dioxo-1,3-diazaspiro[4.5]decan-3-yl)-phenylcarbamate, 3ap. R_f = 0.35 (hex–AcOEt = 70 : 30); FTIR (nujol) *ν* 1675, 1632, 1611 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 9.09 (br s, 1H), 7.28 (m, 9H), 5.11 (s, 2H), 4.38 (d, *J* = 3.8 Hz, 2H), 1.78 (m, 4H), 1.52–1.35 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 173.7, 155.9, 153.2, 138.9, 137.9, 136.1, 131.3, 128.6, 128.3, 127.5, 118.1, 67.0, 45.1, 39.6, 24.6, 24.3; ESI (*m*/*z*) 483.1 [M^+ + H, (100)]; HRMS calcd for [$C_{29}H_{29}N_3O_4$]: 483.2158, found: 483.2155.

1,3-Bis-(4-methoxy-phenyl)-5-phenyl-imidazolidine-2,4-dione, 3aq. R_f = 0.30 (hexane–AcOEt 70 : 30); FTIR (nujol) *ν* 1717.22, 1644.61, 1509.81 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.34 (m, 5H), 6.95 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 5.52 (s, 1H), 3.83 (s, 3H), 3.75 (s, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$) *δ* 159.4, 157.1, 133.2, 129.3, 129.2, 127.7, 127.1, 124.3, 123.0, 114.4, 64.8, 55.5, 55.4; ESI (*m*/*z*) 411.0 [M^+ + Na, (100)], 389.1 [M^+ + 1, (1)]; HRMS calcd for [$C_{23}H_{20}N_2O_4$]: 388.1423, found: 388.1425.

5-(4-Fluoro-phenyl)-1,3-bis-(4-methoxy-phenyl)-imidazolidine-2,4-dione, 3ar. R_f = 0.20 (hexane–AcOEt 70 : 30); FTIR (nujol) *ν* 1774, 1717, 1509 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.36 (m, 6H), 7.07 (m, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 5.51 (s, 1H), 3.83 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 169.2, 164.4, 160.5 (d, *J* = 242.4 Hz), 157.2, 153.9, 128.8 (d, *J* = 8.5 Hz), 127.61, 124.14, 123.09, 116.3 (d, *J* = 22.0 Hz), 114.50, 114.47, 64.05, 55.49, 55.40; ^{19}F-NMR (470.6 MHz) *δ* −112.9 (m, 1F); ESI (*m*/*z*) 428.9 [M^+ + Na, (100)], 407.0 [M^+ + 1, (28)]; HRMS calcd for [$C_{23}H_{19}FN_2O_4$]: 406.1329, found: 406.1326.

5-Biphenyl-4-yl-1,3-bis-(4-methoxy-phenyl)-imidazolidine-2,4-dione, 3as. R_f = 0.15 (hexane–AcOEt 80 : 20); FTIR (nujol) *ν* 1717, 1510 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.60 (d, *J* = 7.9 Hz, 2H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.41 (m, 9H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.57 (s, 1H), 3.83 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 168.7, 162.1, 140.2, 132.1, 128.8, 128.0, 127.7, 127.5, 127.1, 123.0, 114.5, 64.5, 55.5, 55.4; ESI (*m*/*z*) 487.1 [M^+ + Na, (100)]; HRMS calcd for [$C_{29}H_{24}N_2O_4$]: 464.1736, found: 464.1733.

1,3-Bis-(4-methoxy-phenyl)-5-methyl-5-phenyl-imidazolidine-2,4-dione, 3at. R_f = 0.42 (hexane–AcOEt 80 : 20); FTIR (nujol) *ν* 1697, 1648, 1508 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.63 (d, *J* = 8.9 Hz, 2H), 7.41 (m, 5H), 7.19 (d, *J* = 8.9 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (62.3 MHz, $CDCl_3$) *δ* 172.5, 159.4, 156.2, 146.3, 137.9, 137.4, 128.8, 128.0, 124.7, 124.5, 114.3, 113.9, 85.3, 55.4, 55.3, 28.3, 25.5; ESI (*m*/*z*) 425.0

[M^+ + Na, (100)], 403.0 [M^+ + 1, (30)]; HRMS calcd for [$C_{24}H_{22}N_2O_4$]: 402.1580, found: 402.1581.

1,3-Bis-(4-methoxy-phenyl)-5,5-diphenyl-imidazolidine-2,4-dione, 3au. R_f = 0.50 (hexane–AcOEt 70 : 30); FTIR (nujol) ν 1701, 1513, 1508 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.9 Hz, 4H), 7.42 (m, 8H), 7.22 (d, J = 8.9 Hz, 2H), 7.01 (d, J = 8.9 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 3.84 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (62.3 MHz, $CDCl_3$) δ 170.6, 159.6, 156.3, 145.9, 137.7, 137.3, 129.0, 128.7, 128.2, 126.3, 124.7, 114.4, 114.0, 88.2, 55.5, 55.4; ESI (m/z) 487.0 [M^+ + Na, (100)], 465.0 [M^+ + 1, (19)]; HRMS calcd for [$C_{29}H_{24}N_2O_4$]: 464.1736, found: 464.1739.

5-Ethyl-1,3-bis(4-methoxyphenyl)imidazolidine-2,4-dione, 3av. R_f = 0.36 (hex–AcOEt = 70 : 30); FTIR (nujol) ν 1721, 1635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 11.4 Hz, 2H), 7.27 (d, J = 11.4 Hz, 2H), 6.90 (d, J = 11.6 Hz, 2H), 6.88 (d, J = 11.6 Hz, 2H), 4.57 (dd, J = 5.3 and 3.2 Hz, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 2.01 (m, 1H), 1.84 (m, 1H), 0.84 (t, J = 7.4 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.4, 159.3, 157.6, 154.1, 128.3, 127.6, 124.4, 124.3, 114.8, 114.6, 114.4, 114.2, 61.1, 55.5, 21.9, 7.1; ESI (m/z) 341.0 [M^+ + H, (5)], 363.0 [M^+ + Na, (100)]; HRMS calcd for [$C_{19}H_{20}N_2O_4$]: 340.1423, found: 340.1420.

1,3-Bis(4-methoxyphenyl)-5,5-dimethylimidazolidine-2,4-dione, 3aw. R_f = 0.16 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1707, 1633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 9.1 Hz, 2H), 7.14 (d, J = 9.1 Hz, 2H), 6.91 (d, J = 7.4 Hz, 2H), 6.88 (d, J = 7.4 Hz, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 1.43 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 175.5, 159.6, 159.1, 154.4, 130.5, 127.5, 126.3, 124.5, 114.8, 114.3, 63.3, 55.5, 23.9; ESI (m/z) 341.0 [M^+ + H, (100)], 363.0 [M^+ + Na, (100)]; HRMS calcd for [$C_{19}H_{20}N_2O_4$]: 340.1423, found: 340.1422.

2-Bromo-*N*-cyclohexyl-*N*-(cyclohexylcarbamoyl)butanamide, 6a. R_f = 0.65 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1717, 1612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.08 (bs, 1H), 4.30 (t, J = 7.1 Hz, 1H), 4.08 (t, J = 11.4 Hz, 1H), 3.70 (m, 1H), 2.15 (m, 1H), 2.01 (m, 3H), 1.73 (m, 11H), 1.31 (m, 7H), 0.97 (t, J = 7.2 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.9, 153.1, 55.4, 50.3, 47.9, 32.7, 32.1, 30.9, 30.5, 28.6, 25.9, 25.3, 25.3, 24.6, 12.0; ESI (m/z) 293.3 [(M − HBr)$^+$ + H, (100)], 395.1 [M^+ + Na, (40)], 397.1 [(M + 2)$^+$ + Na, (40)]; HRMS calcd for [$C_{17}H_{29}BrN_2O_2$]: 372.1412, found: 372.1415.

2-Bromo-*N*-cyclohexyl-*N*-(cyclohexylcarbamoyl)-2-methylpropanamide, 6b. R_f = 0.55 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1725, 1663 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.33 (d, J = 7.4 Hz, 1H), 4.23 (m, 1H), 3.69 (m, 1H), 2.00 (s, 6H), 1.74 (m, 10H), 1.27 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.3, 153.5, 59.6, 57.3, 50.3, 32.6, 32.4, 30.7, 26.1, 25.5, 25.4, 24.6; ESI (m/z) 293.2 [(M − HBr)$^+$ + H, (100)], 395.1 [M^+ + Na, (70)], 397.1 [(M + 2)$^+$ + Na, (70)]; HRMS calcd for [$C_{17}H_{29}BrN_2O_2$]: 372.1412, found: 372.1411.

1-Bromo-*N*-cyclohexyl-*N*-(cyclohexylcarbamoyl)cyclohexanecarboxamide, 6c. R_f = 0.61 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1709, 1627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.14 (d, J = 6.9 Hz, 1H), 4.17 (t, J = 11.7 Hz, 1H), 3.58 (m, 1H), 2.21 (m, 2H), 2.09 (m, 2H), 1.89 (m, 2H), 1.72 (t, J = 13.6 Hz, 4H), 1.61 (m, 5H), 1.49 (m, 4H), 1.28 (m, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 168.3, 153.3, 67.3, 56.8, 50.3, 39.3, 32.3, 30.5, 26.0, 25.4, 25.3, 24.8, 24.6, 24.2; ESI (m/z) 413.1 [M^+ + H, (5)], 415.1 [(M + 2)$^+$ + H, (5)], 435.0 [M^+ + Na, (90)], 437.0 [(M + 2)$^+$ + Na, (100)]; HRMS calcd for [$C_{20}H_{33}BrN_2O_2$]: 412.1725, found: 412.1722.

2-Bromo-2-phenyl-*N*-*p*-tolyl-*N*-(*p*-tolylcarbamoyl)acetamide, 6d. R_f = 0.30 (hexane–AcOEt = 90 : 10); FTIR (nujol) ν 2917, 1696, 1682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.1 (br s, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.34 (m, 9H), 7.12 (d, J = 8.9 Hz, 2H), 5.42 (s, 1H), 2.46 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.5, 151.4, 139.9, 135.0, 134.8, 134.4, 133.9, 130.4, 129.5, 129.1, 128.9, 128.8, 120.2, 47.4, 21.3, 20.8; ESI (m/z) 438.0 [M^+ + 3, (87)], 437.0 [M^+ + 1, (87)], 457.0 [M^+ − HBr, (100)]; HRMS calcd for [$C_{23}H_{21}BrN_2O_2$]: 436.0786, found: 436.0785.

2-Bromo-*N*-phenyl-*N*-(phenylcarbamoyl)butanamide, 6e. R_f = 0.44 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 2916, 1696, 1665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.22 (bs, 1H), 7.48 (m, 5H), 7.26 (m, 4H), 7.04 (t, J = 7.4 Hz, 1H), 3.91 (t, J = 7.4 Hz, 1H), 2.12 (m, 1H), 1.89 (m, 1H), 0.86 (t, J = 7.3 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 173.2, 151.5, 137.4, 137.0, 129.8, 129.6, 129.2, 129.0, 124.4, 120.2, 47.0, 28.2, 12.0; ESI (m/z) 281.0 [(M − HBr)$^+$ + H, (10)], 361.0 [M^+ + H, (5)], 363.0 [(M + 2)$^+$ + H, (5)], 383.0 [M^+ + Na, (100)], 385.0 [(M + 2)$^+$ + Na, (95)]; HRMS calcd for [$C_{17}H_{17}BrN_2O_2$]: 360.0473, found: 360.0478.

1-Bromo-*N*-phenyl-*N*-(phenylcarbamoyl)cyclohexanecarboxamide, 6f. R_f = 0.43 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1722, 1611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.09 (s, 1H), 7.48 (m, 2H), 7.44 (m, 2H), 7.38 (m, 3H), 7.24 (t, J = 8.0 Hz, 2H), 7.03 (t, J = 8.0 Hz, 1H), 1.81 (m, 2H), 1.72 (m, 2H), 1.52 (m, 2H), 2.76 (m, 4H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 173.9, 152.8, 137.6, 136.9, 130.9, 129.5, 129.0, 128.6, 124.7, 124.3, 120.3, 120.1, 67.0, 53.4, 39.7, 38.1, 24.7, 24.7, 24.5, 22.8; ESI (m/z) 343.0 [(M − HBr)$^+$ + Na, (100)], 422.9 [M^+ + Na, (80)]; HRMS calcd for [$C_{20}H_{21}BrN_2O_2$]: 400.0786, found: 400.0788.

***N*-(Benzylcarbamoyl)-2-bromo-*N*-*tert*-butylbutanamide, 6g.** R_f = 0.40 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1734, 1627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 5H), 6.04 (bs, 1H), 4.39 (d, J = 5.9 Hz, 2H), 3.97 (t, J = 7.2 Hz, 1H), 1.99 (m, 1H), 1.83 (m, 1H), 1.39 (s, 9H), 0.80 (t, J = 7.3 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.7, 144.6, 136.3, 129.0, 128.3, 127.7, 80.0, 52.5, 43.5, 30.4, 24.7, 8.0; ESI (m/z) 275.0 [(M − HBr)$^+$ + H, (20)], 355.0 [M^+ + H, (5)], 357.0 [(M + 2)$^+$ + H, (5)], 376.9 [M^+ + Na, (100)], 378.9 [(M + 2)$^+$ + Na, (100)]; HRMS calcd for [$C_{16}H_{23}BrN_2O_2$]: 354.0943, found: 354.0944.

***N*-(Benzylcarbamoyl)-2-bromo-*N*-phenylbutanamide, 6i.** R_f = 0.41 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1753, 1646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.22 (bs, 1H), 7.41 (d, J = 6.5 Hz, 4H), 7.29 (m, 3H), 7.24 (m, 3H), 4.45 (dd, J = 5.5 and 2.7 Hz, 2H), 3.90 (t, J = 7.3 Hz, 1H), 2.05 (m, 1H), 1.85 (m, 1H), 0.83 (t, J = 7.3 Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 172.6, 154.3, 137.8, 137.4, 129.6, 129.3, 129.2, 128.7, 127.8, 127.5, 47.1, 44.8, 28.1, 11.9; ESI (m/z) 295.1 [(M − HBr)$^+$ + H, (20)],

375.0 [M^+ + H, (25)], 377.0 [$(M + 2)^+$ + H, (30)], 397.0 [M^+ + Na, (90)], 399.0 [$(M + 2)^+$ + Na, (100)]; HRMS calcd for [$C_{18}H_{19}BrN_2O_2$]: 374.0630, found: 374.0633.

***N*-(Benzylcarbamoyl)-2-bromo-2-methyl-*N*-phenylpropanamide, 6j.** R_f = 0.29 (hex–AcOEt = 80 : 20); FTIR (nujol) ν 1754, 1629 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.00 (bs, 1H), 7.45 (m, 5H), 7.36 (m, 5H), 4.52 (d, J = 5.5 Hz, 2H), 1.68 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 173.8, 155.3, 137.8, 137.4, 131.1, 129.5, 129.2, 128.9, 128.6, 128.5, 127.8, 127.4, 127.1, 126.7, 126.1, 59.6, 45.0, 33.1; ESI (m/z) 295.1 [$(M - HBr)^+$ + H, (30)], 396.9 [M^+ + Na, (98)], 398.9 [$(M + 2)^+$ + Na, (100)]; HRMS calcd for [$C_{18}H_{19}BrN_2O_2$]: 374.0630, found: 374.0627.

General procedure for the N^3-*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 r.t., diluted with a 5% $NaHCO_3$ aqueous solution until basic and extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. When necessary, the crude was purified by flash chromatography.

1-*cyclo*-Pentyl-5-phenylimidazolidine-2,4-dione, 14. R_f = 0.34 (hex–AcOEt = 50 : 50); FTIR (nujol) ν 1685, 1623 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (br s, 1H), 7.41 (m, 5H), 4.94 (s, 1H), 4.01 (quintet, J = 8.9 Hz, 1H), 1.88–1.29 (m, 8H); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ 171.2, 155.4, 134.4, 129.3, 128.3, 127.2, 65.3, 55.4, 30.1, 29.1, 23.5, 23.3; ESI (m/z) 245.2 [M^+ + H, (9)], 267.2 [M^+ + Na, (100)]; HRMS calcd for [$C_{14}H_{16}N_2O_2$]: 244.1212, found: 244.1214.

General procedure for the N^1-*p*-benzyl deprotection

To a solution of the hydantoin **3** (1 equiv.) in CH_3CN (0.1 M solution) a solution of CAN (4 equiv.) in water (0.8 M solution) was added dropwise at 0 °C. The temperature was raised to rt and when the starting material disappeared (TLC monitoring) the mixture was diluted with water and extracted with AcOEt. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated under vacuum and the crude purified by flash chromatography.

3-(4-Methoxyphenyl)-5-phenylimidazolidine-2,4-dione, 15. R_f = 0.24 (hex–AcOEt = 50 : 50); FTIR (nujol) ν 1708, 1663 cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ 7.45 (m, 5H), 7.34 (d, J = 9.4 Hz, 2H), 6.98 (d, J = 9.4 Hz, 2H), 5.87 (s, 1H), 3.83 (s, 3H); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ 170.2, 159.9, 131.6, 129.8, 129.2, 127.0, 126.1, 123.4, 79.9, 55.5; ESI (m/z) 283.2 [M^+ + H, (72)], 305.2 [M^+ + Na, (100)]; HRMS calcd for [$C_{16}H_{14}N_2O_3$]: 282.1004, found: 282.1001.

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