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Tailored Aza-Michael Addition as Key Step in the Synthesis of 1*H*-imidazo[5,1-*c*][1,4]oxazine Scaffolds

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A novel protocol for the efficient synthesis of 1*H*-imidazo[5,1-*c*][1,4]oxazines has been developed. Aza-Michael addition of selected primary amines to 1,2-diaza-1,3-dienes (DDs) combined with isothiocyanates or isocyanates in sequential 3-CR process, affords 2-thiohydantoins and hydantoins with suitably positioned functional groups to be used for chemoselective acid-promoted ring-fused formation.

Introduction

Nitrogen and oxygen containing heterocyclic compounds are very important building blocks in medicinal chemistry. In this contest, morpholine is an outstanding heterocyclic motif with wide ranges of pharmacological activities, so a number of molecules possessing a morpholine skeleton are clinically approved drugs.[1]

For example, morpholine condensed heterocycles are of chemotherapeutic value as enzyme inhibitory activities and as γ-secretase modulator (GSM).[2]

On the other hand, substituted (thio)hydantoins are themselves important as they exhibit pharmacological activities against, for example, cancers, microbial infections, metabolic diseases, and epilepsy.[3]

The generation of ring-fused morpholine and 2-thiohydantoin or hydantoin skeletons as amalgamation of these two important pharmacophores, has a particular appeal due to their resemblance to drug-like molecules (Figure 1). Although scarcely represented in the literature,[4] this type of fused-heterobicycle has been documented as mGluR4 allosteric potentiators[5] and as herbicides.[6]

For the 1*H*-imidazo[5,1-*c*][1,4]oxazine scaffolds (Figure 1C), two viable pathways can be conceived: one which involves the construction of the imidazole nucleus (Figure 1A) after the formation of the morpholine the other which involves the formation of the morpholine framework (Figure 1B) starting from the imidazole cycle (Figure 1A).

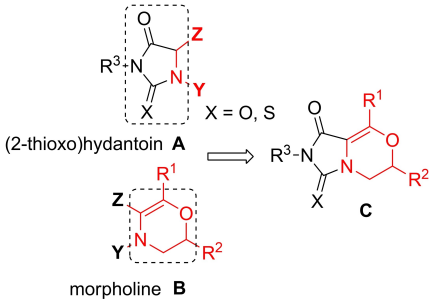

Figure 1. Two alternative pathways in the synthesis of ring-fused system **C**: starting from **A** or from **B**.

However, the use of preformed morpholine scaffold for the synthesis of the chimeric morpholine-hydantoin structure remains the privileged one. In the absence of a general and rapid approach capable to generate condensed-morpholine ring from acyclic precursors owned by 2-thiohydantoins or hydantoins, we became interested in exploring a pathway to tackle this challenge.

Although many ways to assemble diverse ring-fused heterocyclic architectures that exhibit drug activities in human diseases can be referred to cycloaddition-based strategy,[7] and transition-metal-mediated annulations,[8] multicomponent reactions (MCRs)[9] combined with secondary transformations[10,11] seem to be the most promising.

MCRs which combine at least three reactants, simultaneously or in sequence, in one-pot process to generate a product containing most or all atoms of the starting materials, represent a powerful tool since they insure high atom- and step economy, efficiency, mild conditions, high convergence, diversity-oriented synthesis, and library generation.

As such, multicomponent approaches are ideal to address some of the drawbacks affecting classical heterocyclic syntheses, such as poor availability of starting materials or the need for difficult, lengthy, and elaborate synthetic operations.[12] If MCRs are able to rigidify the acyclic reagents into heterocyclic species, the internal presence in such entities of functional

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groups to be converged, may use in further ring-forming process able to increase molecular diversity and complexity.[13,14]

Over the past decade our research group has successfully developed a 3-CR assembly process for 2-thiohydantoins and hydantoins substituted on both nitrogen atoms[15] in virtue of their application in pharmaceuticals, cosmetics and insecticides.[16–18]

To continue our research theme of developing robust methodologies with high user uptake in the pharmaceutical field, we wanted to evaluate the feasibility of assembling the target product through sequential one-pot 3-CR synthesis of 2-thiohydantoin and hydantoin derivatives endowed with useful functionalities for further manipulation. We now report the successful realization of this goal.

To reach the purpose by coupling 1,2-diaza-1,3-dienes (DDs), primary amines and isothiocyanates or isocyanates for the formation of 2-thiohydantoin and hydantoins, respectively, the idea was to carefully select the primary amine derivative bearing a secondary nucleophile group that serves as a handle to be used in further ring-forming reaction (Figure 2).

Results and Discussion

Inspired by our previous findings,[15] DDs **1a–e** (1 equiv.), well-known as Michael acceptors[19] by the presence of the azo electron-withdrawing group in the conjugated system, were reacted with 2-aminoethanol (**2a**) (1 equiv.) or 1-aminopropan-2-ol (**2b**) (1 equiv.) at room temperature to form the key intermediate *N*-adduct **I** that may be quickly elaborated by ring-forming reaction.

In fact, the hydroamination of isothiocyanates **3a–f** (1 equiv.) or isocyanates **3g–j** (1 equiv.) carried out by **I** in neutral conditions, generated intermediate **II**. The spontaneous regioselective heteroring closure by nucleophilic attack of the thioamide or amide NH at the ester function positioned at C-4 of the starting azo-ene system, produced the imidazo chemotype **4a–o** with satisfactory to very good yields (34–89%) (Table 1) offering direct functionalization by 2-hydroxyethyl or 2-hydroxypropyl chain at N-3 of the nitrogen heterocycle.

The reaction conditions were slightly different and substantially concerned the solvent of the reaction as DCM for obtaining **4a–j** was replaced by EtOH in the case of **4k–o** as we previously experienced when isocyanates were used.[15a]

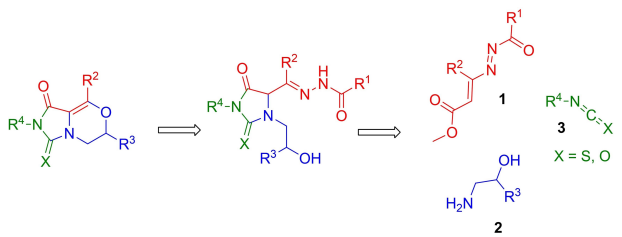
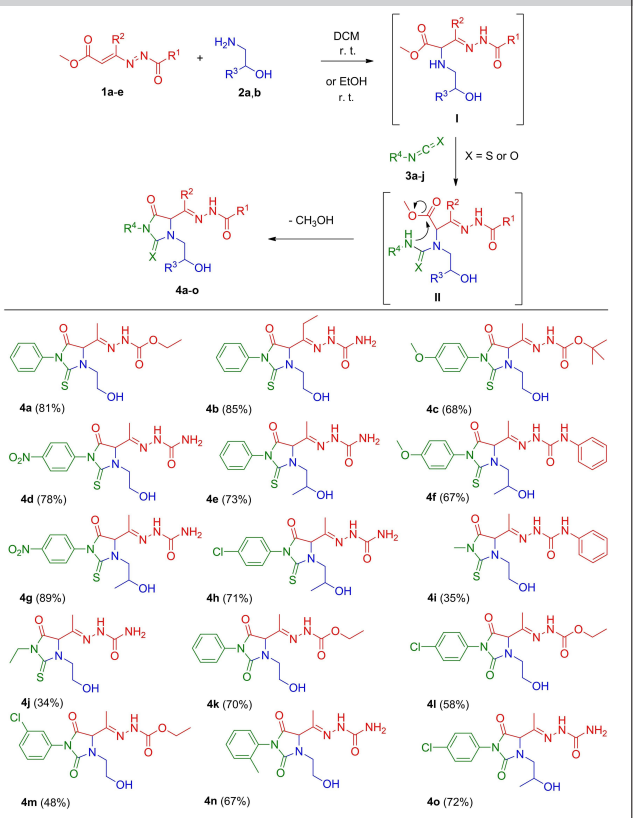


Figure 2. Retrosynthetic analysis towards imidazo[5,1-*c*][1,4]oxazine scaffolds.

Table 1. Substrate scope in the synthesis of 2-thioimidazo **4a–j** and imidazo derivatives **4k–o**.[a,b]



[a] In the case of isothiocyanates DCM was the best reaction solvent, replaced by EtOH in the case of isocyanates. [b] The isolated yields are shown in the brackets.

Since different hydrazide residues bonded at N-1 of DD **1** do not influence the formation of the *N*-adduct, in any case almost quantitative, and the use of aromatic isothiocyanates or isocyanates gives good yields of **4**, the poor yields observed for **4i,j** could be due to the presence of an alkyl substituent on the heteroallene making the nucleophilic addition less effective (Table 1).

Given the coexistence and proximity of one masked acyl group on the side chain at C-4 and of one nucleophilic hydroxy function on the side chain at N-3 of the five-membered heterocycle formed by the 3-CR process, we postulated that the removal of hydrazide moiety in acidic conditions could have promote intramolecular hemi-acetalization as a key step for fused-morpholine ring formation.

Taking into account the role played by heterogeneous catalysis in modern organic synthesis[20] and keeping in mind our recent results,[15a,21] to pursuit the goal we chosen **4a** as model to find the best conditions for its conversion into the corresponding imidazo[5,1-*c*][1,4]oxazine derivative by use of solid acid as Amberlyst 15H[22] varying both solvents and temperatures of the reactions (Table 2).

At first, we attempted to explore the classical hydrolytic cleavage of the hydrazide moiety applying the conditions successfully used for similar substrates[15a] (Table 2, entry 1).

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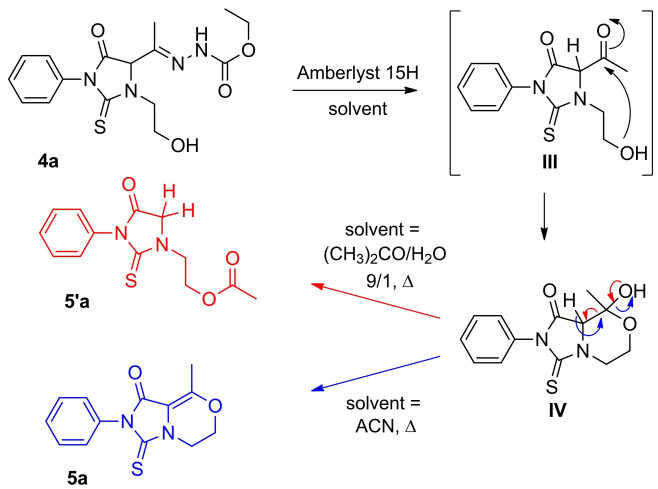
Table 2. Reaction conditions for the morpholine-fused cyclization process of **4a** into **5a**.

Entry[a]	Solvent	Temp [°C]	Amberlyst 15H [equiv.]	Time [h]	Yield of **5a**[b] [%]
1	$CO(CH_3)_2$/H_2O 9/1 (v/v)	70	1.0	7	–
2	DCM	20	0.5	120	traces
3	DCM	reflux	0.5	72	29[c]
4	DCM	reflux	1.0	72	35[c]
5	$CHCl_3$	reflux	0.5	72	52[c]
6	$CHCl_3$	reflux	1.0	72	62[c]
7	ACN	reflux	0.5	24	65[d]
8	ACN	reflux	1.0	10	72

[a] The reaction were performed on 1 mmol scale in 20 mL of solvent. [b] Isolated yields of **5a** on starting **4a**. [c] Unreacted starting **4a** was recovered. [d] Intermediate **IV** (see Scheme 1) was also isolated in 8% yield.

With our surprise, after the work-up of the reaction mixture, 2-(4-oxo-3-phenyl-2-thioxoimidazolidin-1-yl)ethyl acetate (**5′a**) (Scheme 1) was recovered in 75% yield deriving by a retro Claisen-type reaction of the bicyclic intermediate **IV**. On the other hand, when 0.5 equiv. of resin in refluxed ACN was used (Table 2, entry 7), the chromatographic separation of the reaction mixture allowed us to isolate **5a** in 65% yield and the cyclic hemi-acetal intermediate **IV** (8%) that was completely converted in **5a** upon treatment with fresh Amberlyst 15H in ACN under reflux (Scheme 1).

As shown in Table 2, the amount of the catalyst and the boiling point of the reaction solvent were crucial for the success of the formation of **5a** in 72% yield and in 10 h (entry 8). Moreover, in boiling ACN, the acidic resin was able, at the same time, to restore the keto function from **4a** (intermediate **III**), activate the carbonyl function in the nucleophilic addition (intermediate **IV**) and promote the dehydration process of **IV** affording the expected imidazo[5,1-*c*][1,4]oxazine derivative **5a** (Scheme 1).



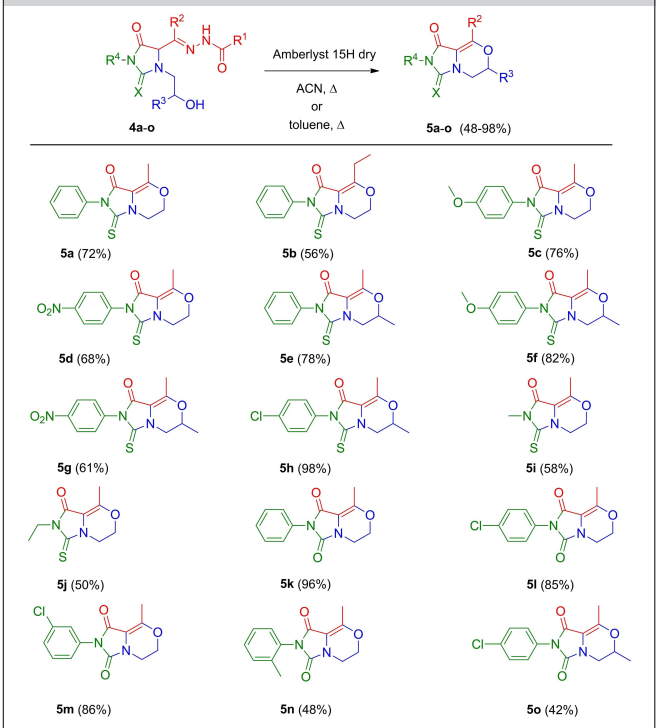
Scheme 1. A possible rationalization of the mechanism for the formation of **IV**, **5′a**, and **5a**.

Accordingly, also **4k**, formed from phenyl isocyanate (**3g**) (see Supporting Information), was subjected to the same reaction conditions but, due to the long times and to the uncomplete transformation in refluxing ACN, a higher boiling temperature was tested and toluene proved to be the best solvent for obtaining the corresponding **5k**.

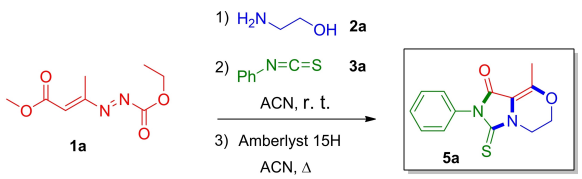
Thus, **4a–j** (1 mmol) were refluxed in ACN (20 mL) in the presence of 500 mg of Amberlyst 15H (dry form, 1 equiv.) for the pertinent reaction time (10–15 h; monitoring by TLC the disappearance of the corresponding **4**) whereas **4k–o** (1 mmol) were treated with the same amount of the resin in refluxing toluene (25 mL), for 12–20 h (by TLC control). After filtration and washing of the resin, the solvent was removed under reduced pressure and the residue was chromatographed (elution mixtures: cyclohexane-ethyl acetate) to provide the 1*H*-imidazo[5,1-*c*][1,4]oxazine derivatives **5a–o** (48–98%) (Table 3).

Finally, we dealt with the development of the one-pot/cascade assembly of **5a** by sequential 3-CR synthesis of **4a** followed by acid-promoted post-cyclization transformation and further internal ring-forming reaction (Scheme 2).

Table 3. Substrate scope of the acid-promoted synthesis of 1*H*-imidazo[5,1-*c*][1,4]oxazines **5a–o**.[a]



[a] The isolated yields are shown in the brackets.



Scheme 2. Sequential 3-CR/cascade fused-heteroannulation process.

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So, DD **1a** (1 mmol) was dissolved in 10 mL of ACN adding 1 equiv. of 2-aminoethanol (**2a**) at room temperature under magnetic stirring. The discoloration of the reaction mixture from red to pale yellow (1 h) attested the formation of the pertinent *N*-adduct **I** and then *N*-phenylisothiocyanate (**3a**) (1 equiv.) was added. The reaction was left at room temperature for 10 h when **4a** was formed (TLC check). At this stage, 10 mL of ACN and 1 equiv. of Amberlyst 15H (dry form) were added and the reaction mixture was refluxed for 10 h. After the removal of the resin by filtration and solvent in vacuo, the residue was purified by column chromatography to afford **5a**.

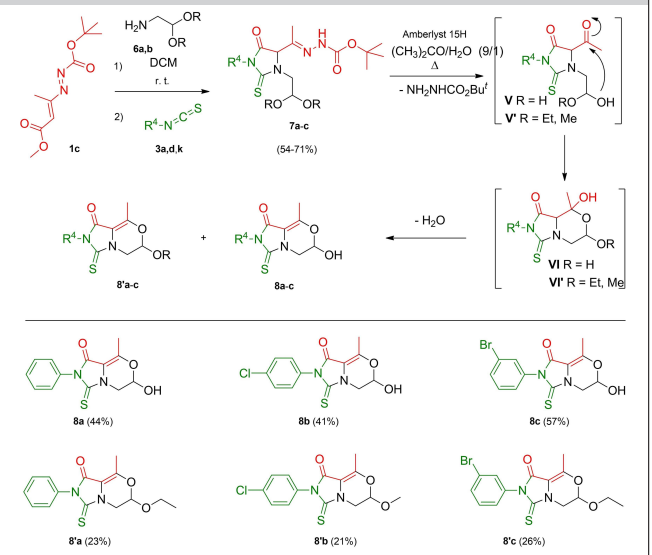
Notably, during this one-pot synthetic operation, four new chemical bonds and two rings were formed yielding **5a** in 53%. With our pleasure, despite the five steps of the overall reaction, the yield was almost comparable with that obtained by means of each single cyclization step indicating that the process could be developed, without the separation of the intermediates, for possible large-scale application.

Aiming to expand the scope of the methodology elaborated in this work, we thought that a planned positioning of a second protected carbonyl group derived from 2,2-dialkoxyethanamine **6a**,**b** in the *N*-aminohydrazone skeleton could have increased the variability of the substituents on the morpholine portion of the ring-fused heterocycles.

By the same 3-CR methodology, DD **1c** (1 mmol) was reacted with 2,2-diethoxyethanamine (**6a**) or 2,2-dimethoxyethanamine (**6b**) (1 mmol) in DCM (10 mL) to form the *N*-aminohydrazone derivative that was coupled with isothiocyanates **3a**,**d**,**k** at room temperature yielding the corresponding substituted thiohydantoins **7a–c** (12–18 h) obtained after chromatographic purification in 54–71% yields (Table 4).

As shown in Table 4, compounds **7a–c** (1 mmol) were then subjected to treatment with Amberlyst 15H (dry form, 500 mg, 1 equiv.) in acetone/water (9:1, 20 mL) under reflux. Unexpectedly, analogous compound of **5′** was not observed under these reaction conditions, whereas aqueous acidic environment simultaneously promotes the hydrolysis of the hydrazone function,[23] and both the formation of the open-chain hemiacetal (**V**), as well as the aldehyde hydrate (**V′**).[24] Any one of these intermediates conceivably evolves in reasonably rapid morpholine-ring formation: the intramolecular ring-closure by nucleophile hydroxy group of both of the intermediates to the restored keto function gives rise to **VI** and **VI′** whose dehydration affords **8a–c** (57-41%) and **8′a–c** (21–26%), respectively.

Table 4. Synthesis of 1*H*-imidazo[5,1-*c*][1,4]oxazine derivatives diversified on the morpholine portion of the bicyclic skeleton.[a]



[a] The isolated yields are shown in the brackets.

Conclusion

In conclusion, we have developed a novel variant for the synthesis of an array of imidazo[5,1-*c*][1,4]oxazine chemotypes by a combination of 3-CR in heteroring-forming, post-cyclization transformation followed by intramolecular fused-heterocycles formation process.

The strategy conceives a careful selection of the starting components to generate intermediate by initial *N*-nucleophilic addition of *N*,*O*-dinucleophiles, such as β-amino alcohols or α-amino acetals, to the heterodiene system of DD affording the *N*-aminohydrazone as the real key intermediate of the whole process. Besides, the choice of heterogeneous acid catalyst Amberlyst 15H in the fused heterocyclic cores formation, offers several benefits including safety in use, rapid removal, easy regeneration making it eco-friendly.

Furthermore, we have reported the realization of the goal directly through the one-pot cascade reactions assembly of **5a** unaffecting its yield in view of large scale application. Some of the synthesized compounds will be evaluated for their biological properties the results of which will be reported in due course.

Experimental Section

General remarks

All the commercially available reagents **2a**,**b**, **3a–k**, **6a**,**b** and solvents were used without further purification. 1,2-Diaza-1,3-dienes **1a–e** were synthesized as a mixture of *E/Z* isomers as previously reported.[19a,25] Chromatographic purification of compounds was carried out on silica gel (60–200 μm). TLC analysis was performed on pre-loaded (0.25 mm) glass supported silica gel plates (Kieselgel 60); compounds were visualized by exposure to UV light and by dipping the plates in 1% $Ce(SO_4)\cdot 4H_2O$, 2.5% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ in 10% sulfuric acid followed by heating on a hot plate. Melting points were determined in open capillary tubes with a Gallenkamp apparatus and are uncorrected. FT-IR spectra were obtained as Nujol mulls and recorded on Nicolet Impact 400. All ^1H NMR, ^{13}C NMR spectra and 2D experiments were recorded on Bruker Avance at 400 and 100 MHz, respectively, using [D_6]DMSO as solvent. Chemical shift (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent and are sorted in ascending order within each group. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet,

q = quartet, m = multiplet and br = broad signal, Ar, aromatic hydrogen. All coupling constants (*J* value) are given in Hertz [Hz]. All the OH, NH and NH_2 exchanged with D_2O. The multiplicities in ^{13}C NMR spectra were obtained using HMQC experiments to aid in assignment (q = methyl, t = methylene, d = methine, s = quaternary). In some spectra double peaks are due to *E/Z* isomerism or to a mixtures of diastereomers. High-and low-resolution mass spectroscopy was performed on a Micromass Q-ToF Micro mass spectrometer (Micromass, Manchester, UK) using an ESI source. Elemental analyses were within ±0.4 of the theoretical values (C, H, N).

MCR procedure for the synthesis of substituted 2-thiohydantoins 4 a–j

To a solution of DD **1 a**–**e** (1 mmol) in DCM (10 mL) at room temperature, β-aminoalcohol **2 a**,**b** (1 mmol) was added and the reaction mixture was stirred at room temperature until the disappearance of the corresponding DD and the formation of the *N*-adduct (TLC check, 0.5–2 h). Directly to the reaction medium, 1 equiv. of isothiocyanate **3 a**–**f** was then added, and the reaction was left at room temperature under magnetic stirring (14–18 h). Then the solvent was removed under reduced pressure and the residue was chromatographed on silica gel column (elution mixture of cyclohexane/ethyl acetate, from 60/40 to pure ethyl acetate). The collected **4 a**–**j** were precipitated from ethyl acetate/petroleum ether and crystallized from appropriate solvents. Compounds **4 f**–**h** were obtained as a mixture of diastereomers (see Supporting Information) and were used as such for their further transformation.

MCR procedure for the synthesis of substituted hydantoins 4 k–o

To a solution of DD **1 a**,**d** (1 mmol) in EtOH (10 mL) at room temperature, β-aminoalcohol **2 a**,**b** (1 mmol) was added and the reaction mixture was stirred at room temperature until the disappearance of the corresponding DD and the formation of the *N*-adduct (TLC check, 0.5–2 h). Directly to the reaction medium, 1 equiv. of isocyanate **3 g**–**j** was then added, and the reaction was left at room temperature under magnetic stirring (20–24 h). Then, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel column (elution mixture of cyclohexane/ethyl acetate, from 60/40 to pure ethyl acetate). The collected **4 k**–**o** were precipitated from ethyl acetate/petroleum ether and crystallized from appropriate solvents. Compound **4 o** was obtained as a mixture of diastereomers (see Supporting Information) and was used as such for its further transformation.

Procedure for the synthesis of the 1H-imidazo[5,1-c][1,4]oxazine derivatives 5 a–o from 4 a–o

To 2-thiohydantoin derivatives **4 a**–**j** (1 mmol) dissolved in ACN (20 mL), Amberlyst 15H (500 mg in dry form;) was added and the reaction was refluxed for the appropriate reaction time established by the disappearance of starting materials **4a**–**j** (monitored by TLC) and the formation of the corresponding **5 a**–**j**. In the case of hydantoins derivatives **4 k**–**o**, 1 mmol was dissolved in toluene (25 mL), added of Amberlyst 15H (500 mg in dry form) and refluxed for the pertinent reaction time for their complete conversion into **5 k**–**o** (checked by TLC). In any case, once the reaction was over, the resin was filtered off and washed with ethyl acetate. Then, the combined filtrate was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (elution mixture of cyclohexane/ethyl acetate, from 70/30 to 50/50) to furnish pure **5 a**–**o** that were crystallized from appropriate solvents.

One pot procedure for the synthesis of 1H-imidazo[5,1-c][1,4]oxazine derivative 5 a

The DD **1 a** (1 mmol) was dissolved in 10 mL of ACN in round bottom flask adding 1 equiv. of 2-aminoethanol (**2 a**) at room temperature under magnetic stirring. The discoloration of the reaction mixture from red to pale yellow (1 h) attested the formation of *N*-adduct intermediate **I** so *N*-phenylisothiocyanate (**3 a**) (1 equiv.) was added. The reaction was left at room temperature for 14 h when **4 a** was mostly formed (TLC check). Additional 10 mL of ACN and 500 mg of Amberlyst 15H (dry form) were put in the flask and the reaction mixture was refluxed until the complete disappearance of **4 a** and the formation of **5 a** (10 h; TLC check). Then, the resin was removed by filtration and washed with ethyl acetate. The combined filtrate was evaporated in vacuo and the residue was purified by column chromatography on silica gel (elution mixture: cyclohexane/ethyl acetate, 70/30) to allow pure **5 a** (53 %) that was crystallized from ethyl acetate.

MCR procedure for the synthesis of substituted 2-thiohydantoins 7 a–c

To a solution of DD **1 c** (1 mmol) in DCM (10 mL) at room temperature, 2,2-dialkoxyethanamine derivative **6 a**,**b** (1 mmol) was added and the reaction mixture was stirred at room temperature until the disappearance of **1 c** and the formation of the *N*-adduct (TLC check, 0.5 h). Directly to the reaction medium, 1 equiv. of the pertinent isothiocyanate (**3 a**,**d**,**k**) was then added, and the reaction was left at room temperature under magnetic stirring (12–18 h). In the case of **7 b**, the compound precipitated from DCM and was collected by filtration. In the case of **7 a** and **7 c**, the solvent was removed under reduced pressure and the reaction mixture was chromatographed on silica gel column (elution mixture of cyclohexane/ethyl acetate, from 60/40 to 30/70). The collected **7 a**–**c** were crystallized from appropriate solvents.

Procedure for the synthesis of derivatives 8 a–c e 8′a–c

1 Mmol of **7 a**–**c** was refluxed in 20 mL of acetone/water (9/1, v/v mixture) in the presence of Amberlyst 15H (500 mg, dry form) until the disappearance of the starting materials (8–13 h, checked by TLC). The resin was filtered off and washed with ethyl acetate. The combined filtrate was evaporated in vacuo and the residue was purified by column chromatography on silica gel (elution mixture: cyclohexane/ethyl acetate from 80/20 to 50/50) to obtain **8 a**–**c** and **8′a**–**c**.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Keywords: Fused-ring systems · Hydrazones · Michael addition · Multicomponent reactions · Synthetic methods

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