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# From targeted aza-Michael addition to linked azaheterocyclic scaffolds

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ABSTRACT

A straightforward method for the synthesis of spaced, phenyl-linked bis(thiohydantoin) derivatives and (thio)hydantoins spiro-fused to pyrroline ring has been developed. All the synthetic strategies here presented rely on initial aza-Michael addition followed by acylation/regioselective ring-closure step involving DD, primary amine and iso(thio)cyanate in a 3-CR providing 1,3,5-trisubstituted (thio)hydantoins. The choice of opportune acyclic reagents in the sequential 3-CR followed by 1,4-nucleophilic addition/intramolecular ring closing and 1,3-dipolar cycloaddition permits a number of C–N and C–C formation that realizes different kind of linkage between several pharmacophores.



## 1. Introduction

The structural diversity of natural and synthetic heterocycles has become a key topic in organic, bioorganic and medicinal chemistry. As a result, there is an increasing need to access new areas of chemical space with the aim to discover biologically relevant heterocyclic molecules in a rapid and economic fashion. Multicomponent reactions (MCRs)[1] have gained much importance in synthetic organic chemistry as they produce the target compounds in a single step avoiding the isolation of intermediates. MCRs can use domino reactions or sequential reactions and have proved to be efficient for the construction of many different types of heterocycles.[2]

Specifically hydantoin and 2-thiohydantoin-based scaffolds exhibit a wide array of properties ranging from bioscience materials[3] to bioactive compounds;[4] therefore, numerous synthetic strategies both on solid support[5] and in solution phase[6] have been reported in the literature.

In this field our research group has recently developed a sequential 3-CR to afford selectively substituted hydantoins[7a] and 2-thiohydantoins[7b] from 1,2-diaza-1,3-dienes (DDs)[8] as readily available building blocks.

Since MCRs that afford products with reactive functional groups capable of being utilized in a further reaction are powerful methods for generating diverse collections of functionalized heterocyclic templates,[9] we envisioned the extension of our previous results to allow the synthesis of linked azaheterocyclic architectures.

In a continuation of recent studies, we herein describe synthetic strategy to spiro-fused as well as spaced azaheterocyclic scaffolds based on initial 3-CR.

## 2. Results and discussion

The aza-Michael reaction can be considered a hydroamination process and it has been largely applied to DDs by our group as a strategic starting point to produce different heterocyclic templates.[10] The α-aminohydrazone A, resulted from the nucleophilic addition of primary amine **2** to DD **1**, is a densely functionalized derivative, which accounts for its chemical versatility through the simultaneous presence of both electrophilic (i.e., ester and hydrazone functions) and nucleophilic (i.e., secondary amine) centres (Scheme 1).

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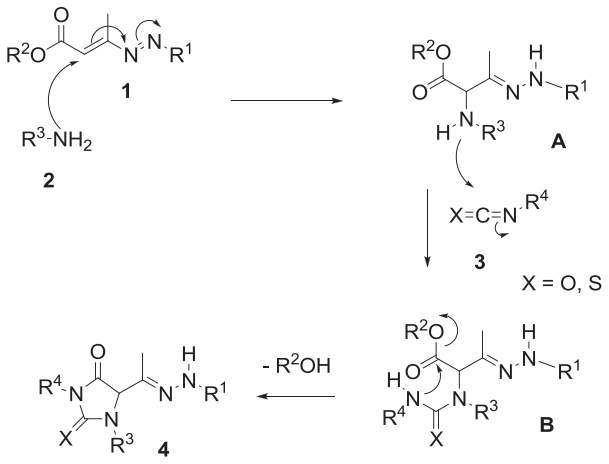
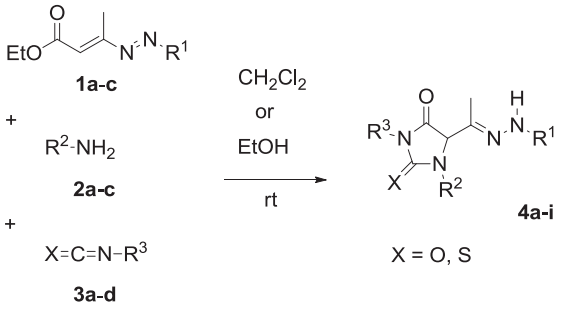


**Scheme 1.** Proposed mechanism for the formation of 1,3,5-trisubstituted hydantoins and 2-thio analogues **4**.

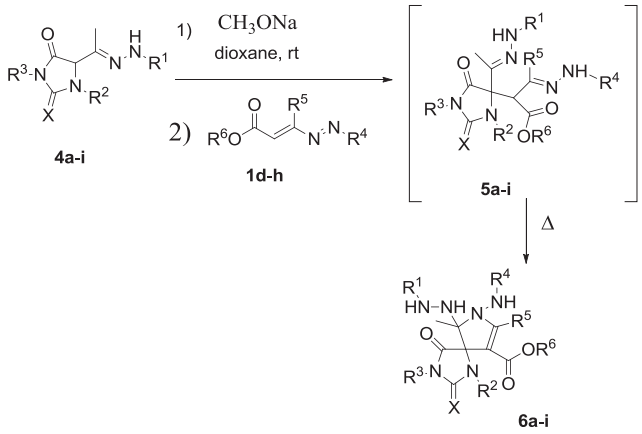
The acylation process involving the secondary amine moiety of **A** with isothiocyanate or isocyanate **3** generates the requisite asymmetric thiourea or urea derivative **B** that in turn provides regioselective nucleophilic attack at the terminal ester function of the azo-ene system of **1** concluding in the 2-thiohydantoin or hydantoin ring **4** formation (Scheme 1).

Using this consolidated sequential 3-CR protocol, regioselectively 1,3,5-substituted hydantoins and 2-thio analogues **4a**–**i** have been successfully prepared in good yields (63–86%) (Scheme 2, Table 1).



**Scheme 2.** Sequential 3-CR protocol leading to 1,3,5-trisubstituted hydantoins and 2-thio analogues **4a**–**i**.

Both the heterocyclic structures possess reactive groups, namely the hydrazone chain at C5-position of the ring, that can be utilized for the preparation of spiro azaheterocyclic architectures. Thus, the base-promoted carbanion formation from **4** in dioxane at room temperature leads to nucleophilic 1,4-addition to another DD **1** molecule affording 5,5-disubstituted intermediate **5** (Scheme 3). By heating the crude reaction mixture, the two hydrazone side chains of **5** co-operate in the heteroannulation process by means of intramolecular nucleophilic attack. According to this synthetic approach, a (thio)hydantoin spiro-fused to a pyrroline ring (Scheme 3) can be generated. So, after removal of dioxane and purification of the crude reaction mixture by flash chromatography, **6a**–**i** were obtained in good yields (60–77%, Table 2). Moreover, this domino process allows diversified substitution pattern at N-1 and N-3 of the 2-thiohydantoin ring of **6a**–**e** with respect to those present in similar compounds obtained from the reactivity of DDs with *N*,*N*′-dialkylthioureas.[11]



**Scheme 3.** Synthetic pathway affording spiro-fused azaheterocycles **6a**–**i**.

The spiro-fused heterobicyclic structure has been confirmed by single-crystal X-ray diffraction study of compound **6c**[12] (Fig. 1) allowing the stereochemical assignment of the two asymmetric carbons. By comparison of the $^1$H NMR chemical shifts values of spiro derivatives **6a**–**i**, C5(*R*/*S*),C6(*R*/*S*) resulted the prevalent diastereomer isolable (60–77%). Only in the case of the reaction affording compound **6c**, it was possible to obtain the minor diastereomer C5(*R*/*S*),C6(*S*/*R*) in very small amount (9%) By virtue of the yields recorded for the major diastereomer of **6a**–**i**, we can conclude that in all cases the reaction proceeds with high diastereoselectivity.

Hence, we reasoned that the propargylic appendage at N-1 of the hydantoin core of **6h**,**i** would give us a handle to enrich the structure with an additional biologically active heterocycle.

Therefore, the optimized[13] Cu$^I$-catalyzed Huisgen 1,3-dipolar cycloaddition involving azides **7a**,**b** and the propargyl function of **6h**,**i** provides 1,4-disubstituted 1,2,3-triazole derivatives **8a**,**b** in

**Table 1**
Results of the synthesis of 1,3,5-trisubstituted 2-thiohydantoin and hydantoin derivatives **4a**–**i**

| Entry | DD **1** | | Amine **2** | | Isothiocyanate or isocyanate **3** | | | Solvent | 2-Thiohydantoin or hydantoin **4** | Yield[a] (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | $R^1$ | | $R^2$ | | X | $R^3$ | | | |
| 1 | **1a** | $CO_2Et$ | **2a** | *n*-Bu | **3a** | S | Ph | $CH_2Cl_2$ | **4a** | 71 |
| 2 | **1b** | $CO_2^tBu$ | **2b** | *n*-Pr | **3b** | S | Me | $CH_2Cl_2$ | **4b** | 63 |
| 3 | **1b** | $CO_2^tBu$ | **2a** | *n*-Bu | **3a** | S | Ph | $CH_2Cl_2$ | **4c** | 69 |
| 4 | **1c** | $CO_2Me$ | **2b** | *n*-Pr | **3b** | S | Me | $CH_2Cl_2$ | **4d** | 64 |
| 5 | **1c** | $CO_2Me$ | **2a** | *n*-Bu | **3a** | S | Ph | $CH_2Cl_2$ | **4e** | 88 |
| 6 | **1a** | $CO_2Et$ | **2a** | *n*-Bu | **3c** | O | Ph | EtOH | **4f** | 67[b] |
| 7 | **1b** | $CO_2^tBu$ | **2b** | *n*-Pr | **3c** | O | Ph | EtOH | **4g** | 76[b] |
| 8 | **1a** | $CO_2Et$ | **2c** | Propargyl | **3d** | O | 3-Cl–Ph | EtOH | **4h** | 63[b] |
| 9 | **1c** | $CO_2Me$ | **2c** | Propargyl | **3c** | O | Ph | EtOH | **4i** | 63[b] |

[a] Yield of pure isolated product.
[b] See Ref. 7a.