Facile regiodivergent synthesis of spiro pyrrole-substituted pseudothiohydantoins and thiohydantoins via reaction of [e]-fused 1H-pyrrole-2,3-diones with thiourea

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Full Research Paper

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Abstract

A highly divergent synthesis of regioisomeric thiohydantoins and pseudothiohydantoins spiro-fused to a pharmacologically valuable pyrrole-2-one fragment involving the reaction of [e]-fused 1H-pyrrole-2,3-diones with thioureas was developed. The obtained spiro pseudothiohydantoin derivatives were found to undergo a pseudothiohydantoin–thiohydantoin rearrangement. The reactions were shown to proceed under catalyst-free conditions in good yields, and the products were isolated without applying preparative chromatography methods.

Introduction

Hydantoin (imidazolidine-2,4-dione) derivatives are omnipresent among biologically active compounds [1]. Many of them are commercially available drugs, for example, anticonvulsants phenytoin [2] and albutoin [3], the muscle relaxant dantrolene [4], or the nonsteroidal antiandrogen agent enzalutamide [5] (Figure 1).

Despite this fact, hydantoin derivatives belong to a special group of scaffolds in medicinal chemistry. Indeed, they are structurally related to rhodanine (2-thioxothiazolidin-4-one), and sometimes are classified as pan-assay interference compounds (PAINS), which are abhorrent in high-throughput screenings [6]. To clarify whether such compounds are privi-
Scheme 2: Syntheses of regioisomeric 5-spiro-substituted thiohydantoins and pseudothiohydantoins: previous [10] and this work.

Spiro heterocycles are relatively new and insufficiently investigated structures in medicinal chemistry [17,18]. The introduction of spiro-fused cyclic moieties in small molecules increases the degree of their structural (shape) complexity, which may lead to the reduced binding promiscuity and improved clinical success [19]. Thus, recent development of 3D modelling methods facilitated investigations on the importance of 3D properties of small-molecular drug candidates [20-22] and inspired chemists to develop diversity-oriented methods for complex 3D molecules [23,24]. Considering that to the best of our knowledge, only a sole report exists [10] that describes the synthesis of regioisomeric 5-spiro-substituted thiohydantoins and pseudothiohydantoins and their PTR (Scheme 2), we were encouraged to develop a divergent synthetic approach to access regioisomeric thiohydantoins and pseudothiohydantoins that are spiro-fused to a pharmacologically valuable pyrrole-2-one fragment and to investigate the scope and conditions of their PTR behavior (Scheme 2).
**Results and Discussion**

1*H*-Pyrole-2,3-diones fused at [ε]-side (FPDs) 1 can be viewed as a versatile polyelectrophilic synthetic platform (Figure 2), enabling facile preparation of libraries of heterocyclic molecules with an emphasis on skeletal diversity from a single set of reagents [25-27].

One of the most intriguing chemical properties of FPDs 1 is their ability to undergo a cyclocondensation with 1,3-binucleophilic reagents to form spiro[4.4] heterocycles bearing a pharmacophoric pyrrole-2-one moiety (Scheme 3) [28,29]. We employed this feature as a key step in the development of a straightforward and concise synthetic approach towards regioisomeric thiohydantoins and pseudothiohydantoins spiro-fused to a pyrrole-2-one fragment.

To test the preparation of the target spiro-fused pseudothiohydantoins and thiohydantoins, we examined the reaction of FPD 1a with thiourea by heating equimolar amounts of the reagents in toluene for 5 min (until the disappearance of the dark violet color of FPD 1a). The reaction mixture was examined by UPLC–MS. Two major products with m/z = 396 ([M + H]⁺, ESI⁺) were observed in a ratio of ≈1:1, which corresponded to adducts of thiourea with FPD 1a. The adducts were isolated, and their structures were elucidated as the desired spiro-fused thiohydantoin 2a and pseudothiohydantoin 3a (Scheme 4).

Possibly, when carrying out the reaction of FPD 1a with thiourea by refluxing the reaction mixture in toluene, part of the product 3a was converted into 2a because of PTR. We assumed that at lower temperatures, the main product of the reaction could be pseudothiohydantoin 3a. To prove this assumption, we examined the reaction of FPD 1a with thiourea at room temperature in various solvents (Table 1).

Obviously, the ratio of products 2a and 3a was dependent not only on the temperature of the reaction, but also on the polarity of the solvent. We found that optimal conditions for dominant formation of pseudothiohydantoin 3a were applied by stirring the reaction mixture at room temperature in ethyl or butyl acetate (Table 1, entries 2 and 6).
Table 1: Reaction of FPD 1a with thiourea at room temperature in various solvents.\textsuperscript{a}

| Entry | Solvent     | 2a:3a\textsuperscript{b} |
|-------|-------------|---------------------------|
| 1     | acetone     | 30:70                     |
| 2     | ethyl acetate | 5:95                     |
| 3     | 1,4-dioxane | 50:50                     |
| 4     | acetic acid | 30:70                     |
| 5     | acetonitrile | 50:50                  |
| 6     | butyl acetate | 5:95                   |
| 7     | toluene     | traces\textsuperscript{c} |

\textsuperscript{a}Reaction mixtures were stirred until the disappearance of the dark violet color of FPD 1a (about 2–4 h). \textsuperscript{b}According to UPLC–MS data. \textsuperscript{c}The reaction proceeded too slowly, and FPD 1a underwent hydrolysis faster than reaction with thiourea (the reaction vessel was contaminated with water during samplings for analyses).

For the development of a convenient procedure for thiohydantoin 2a without isolation of its regioisomer 3a being required, we carried out the reaction of FPD 1a with thiourea in various solvents under reflux (Table 2).

Table 2: Reaction of FPD 1a with thiourea at reflux in various solvents.\textsuperscript{a}

| Entry | Solvent     | 2a:3a\textsuperscript{b} |
|-------|-------------|---------------------------|
| 1     | acetone     | 30:70\textsuperscript{c} |
| 2     | ethyl acetate | 22:78                    |
| 3     | 1,4-dioxane | 90:10\textsuperscript{d} |
| 4     | 1,4-dioxane | 99:1\textsuperscript{d}  |
| 5     | acetic acid | 30:70                     |
| 6     | acetonitrile | 25:75                    |
| 7     | butyl acetate | 95:5                     |
| 8     | toluene     | 50:50\textsuperscript{d} |

\textsuperscript{a}Reaction mixtures were refluxed until the disappearance of the dark violet color of FPD 1a (about 5–15 min). \textsuperscript{b}According to UPLC–MS data. \textsuperscript{c}The reagents were mixed prior to heating. \textsuperscript{d}Thiourea was added to a boiling solution of FPD 1a.

As a result of this optimization, we established that thiohydantoin 2a was formed as major product upon refluxing the reaction mixture in butyl acetate or 1,4-dioxane (Table 2, entries 3, 4, and 7). Interestingly, at different reagent ratios, the yield of compound 2a was affected as well (Table 2, entries 3 and 4). When the reagents were mixed prior to heating (Table 2, entry 3), the yield of compound 2a was lower than when the reagents were mixed in the boiling solvent (Table 2, entry 4). Probably, compound 2a was formed not only as a result of the corresponding PTR, but as a result of a concurrent attack of the amino group of thiourea on the C-3a atom of FPD 1a (Scheme 6).

Next, we examined the influence of substituents in the thiourea motif on its reaction with FPDs 1. It was found that monosubstituted thioureas (N-methylthiourea, N-phenylthiourea, N-(4-chlorophenyl)thiourea, N-(3,5-dimethylphenyl)thiourea, N-(4-nitrophenyl)thiourea, and N-1-naphthylthiourea) reacted with FPD 1a unselectively, forming a mixture of four inseparable adducts (the reaction mixtures were analyzed by UPLC–MS) (Scheme 7). Unfortunately, we did not succeed to find any conditions for a selective formation of either of them.

Unexpectedly, the implementation of N-acetylthiourea in the reaction with FPDs 1, both under conditions A and B (see Ta-
Table 3: Series of spiro-fused thiohydantoins 2a–m and pseudothiohydantoins 3a–m from various FPDs 1a–n.

| Entry | R           | R'        | Yield of 2 (%)\(^{a,b}\) | Yield of 3 (%)\(^{a,c}\) |
|-------|-------------|-----------|---------------------------|---------------------------|
| a     | 2-OH-C₆H₄   | Ph        | 97                        | 79                        |
| b     | 5-Cl-2-OH-C₆H₃ | Ph      | 78                        | 87                        | (CCDC 1952743) |
| c     | 2-OH-C₆H₄   | 4-OMe-C₆H₄ | 79                        | 91                        |
| d     | 2-OH-C₆H₄   | 4-OEt-C₆H₄ | 90                        | 79                        |
| e     | 2-OH-C₆H₄   | 4-Cl-C₆H₄  | 78                        | 61                        |
| f     | 2-OH-C₆H₄   | 4-Br-C₆H₄  | 87                        | 61                        | (CCDC 1952745) |
| g     | 2-OH-C₆H₄   | 4-Me-C₆H₄  | 89                        | 89                        |
| h     | 5-No₂-2-OH-C₆H₃ | Ph      | 95                        | 58                        |
| i     | 2-OH-C₆H₄   | 4-No₂-C₆H₄ | 61                        | 53                        |
| j     | 5-Br-2-OH-C₆H₃ | Ph      | 65                        | 59                        |
| k     | 2-OH-C₆H₄   | 4-F-C₆H₄   | 81                        | 82                        |
| l     | CH₂CH₂OH    | 4-Cl-C₆H₄  | 90                        | 97                        | (CCDC 1952798) |
| m     | CH₂CH₂OH    | 4-Me-C₆H₄  | 98                        | 75                        |
| n     | 2-OH-C₆H₄   | OEt       | -                         | -                         |

\(^a^{Isolated yields.} \(^b^{Conditions A: a mixture of FPD 1a–n (1 mmol) and thiourea (1 mmol) was refluxed in 1,4-dioxane (5 mL) for 4 h.} \(^c^{Conditions B: a mixture of FPD 1a–n (1 mmol) and thiourea (1 mmol) was stirred in ethyl acetate (5 mL) for 12 h at room temperature.}

Scheme 7: Reaction of FPD 1a with monosubstituted thioureas.

\[ R = \text{Me, Ph, 4-Cl-C}_6\text{H}_4, \text{3,5-Me}_2\text{-C}_6\text{H}_5, \text{4-NO}_2\text{-C}_6\text{H}_4, \text{C}_10\text{H}_7 \]

1,3-Dibutylthiourea reacted smoothly at room temperature in ethyl acetate with FPDs 1 to form mixtures of products 5 and 6 (Scheme 8). Moreover, it was observed that the percentage of compounds 5 in reaction mixtures increased over time upon storage of the solutions. As such, 6 readily underwent PTR, affording the corresponding compounds 5, but unfortunately, we did not succeed to isolate pseudothiohydantoins 6.

The reaction of FPDs 1 with 1,3-dibutylthiourea in 1,4-dioxane resulted in exclusive formation of thioureas 5 upon heating at reflux for 2–4 h (Table 5). The facility of thioureas 5 formation could be explained by the electron-donating effect of the butyl substituents, which...
Table 4: Reaction of FPDs 1 with N-acetylthiourea.

| Product | Ar     | R   | Yield of 4 (%) |
|---------|--------|-----|----------------|
| 4a      | Ph     | H   | 80             |
| 4b      | 4-Cl-C_{6}H_{4} | H | 75            |
| 4c      | Ph     | Cl  | 79             |

*Isolated yields. \(^{2}\)CCDC 1952746.

Table 5: Reaction of FPDs 1 with 1,3-dibutylthiourea at reflux.

| Product | Ar     | R   | Yield of 5 (%) |
|---------|--------|-----|----------------|
| 5a      | Ph     | 2-OH-C_{6}H_{4} | 75          |
| 5b      | Ph     | 5-Cl-2-OH-C_{6}H_{3} | 76          |
| 5c      | 4-Cl-C_{6}H_{4} | CH_{3}CH_{2}OH | 76          |

*Isolated yields. \(^{2}\)CCDC 1952744.

Scheme 8: Reaction of FPDs 1 with 1,3-dibutylthiourea at room temperature.

increased the nucleophilicity of the butyl-substituted nitrogen atoms and promoted its attack on the electrophilic center C-3a of FPDs 1.

The reaction of FPDs 1 with 1,3-diphenylthiourea proceeded in a similar manner. Thiohydantoins 7 were predominantly formed when the reaction was conducted at reflux in 1,4-dioxane, and pseudothiohydantoins 8 were formed as main products at room temperature (Table 6).

Notably, the formation of thiohydantoins 7 required longer time in comparison with unsubstituted thiourea and 1,3-dibutylthiourea. Possible reasons for this are the influence of the steric hindrance induced by the phenyl substituents and weakening of the nucleophilic properties of the phenyl-substituted nitrogen atom, which prevented a nucleophilic attack of 1,3-diphenylthiourea on the electrophilic center C-3a of FPDs 1.

The observed PTRs could have proceed through two alternative pathways (Scheme 9), with the first stage being dissociation of the C\_spiro–S bond [32] in pseudothiohydantoins PTThH, affording intermediate A. Then, A could have further undergone either an intramolecular cyclization by NH attack, forming thiohydantoin THH (path A), or further dissociation to FPD 1 and thiourea. The latter would subsequently attack FPD 1 with both nucleophilic NH centers, forming thiohydantoin THH (path B).

Conclusion

In conclusion, we have developed a divergent approach to pharmaceutically interesting regiomeretic thiohydantoins and
pseudothiohydantoins spiro-fused to a pyrrole-2-one fragment via the reaction of \( \ell \)-fused 1\(H \)-pyrrole-2,3-diones with thioureas. The obtained pseudothiohydantoins were found to be prone to undergo a pseudothiohydantoin–thiohydantoin rearrangement. Therein, the substituents of the thiourea moiety were found to be crucial for tuning the conditions of this rearrangement. Notably, the reactions proceeded under catalyst-free conditions with good yields.

### Supporting Information

**Supporting Information File 1**

Experimental details, copies of \(^1H \) and \(^{13}C \) NMR spectra, X-ray crystallographic details, references to antimicrobial assay results, and a detailed revision of previously published structures.

[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-15-280-S1.pdf](https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-15-280-S1.pdf)

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