SIMPLE AND EFFICIENT SYNTHESIS OF 5-SUBSTITUTED-3-PHENYL-2-THIOXOIMIDAZOLIDIN-4-ONE DERIVATIVES FROM S-AMINO ACIDS AND PHENYLISOTHIOCYANATE IN Et$_3$N/DMF-H$_2$O

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GRAPHICAL ABSTRACT

Abstract A concise approach for the transformation of various S-amino acids into the 5-alkyl-3-phenyl-2-thioxoimidazolidin-4-one heterocycles using phenylisothiocyanate is described. Phenylthiohydantoins of amino acid were synthesized at room temperature in Et$_3$N/DMF-H$_2$O with easy workup and excellent yields.

Keywords Amino acids; cyclization; phenylisothiocyanate; 2-thiohydantoin

INTRODUCTION

Thiohydantoins are hydantoin’s analog, in which the carbonyl group is replaced by the thiocarbonyl group, and are pharmaceutically active compounds. There has been considerable interest in 2-thiohydantoins, which display promising biological activities. The derivatives of 3-phenyl-2-thiohydantoins with nonpolar
substituent at the 5-position inhibited the peripheral effect of T4 (Fig. 1, compounds I, II, and III). These derivatives exhibit activities such as anticonvulsant, fungicidal, antimutagenic, anticarcinogenic, antiviral, and immune depressing activities. The treatment of hormone-independent prostate cancers was done by thiodyantoins. In the literature, thiodyantoins derivatives were reported for androgen receptor (AR) agonism and antagonism in human prostate cancer cells (Fig. 1, compounds IV and V).

Owing to N–H···S=C hydrogen bonds or a 1D H-bonded chain with N–H···O=C interactions, they perform energetic balance between H-bonded structures with increased potential for drug polymorph formation. Thiodyantoins have also been used in crystal engineering as spacers in metallo-organic frameworks, chemosensor, polymerization catalysts, corrosion inhibitors, and analytical reagents. The thiodyantoins derived from amino acids were used for the stepwise sequence analysis of the peptide or the protein from the carboxyl termini.

To improve the efficiency of PTH-amino-acid synthesis, several attempts have been carried out and encouraging results were obtained. The reaction has been conducted with amino acid in the presence of KOH/EtOH, Na2CO3/dioxane, KOH/EtOH/AcOH, ionic liquid, NaOH/water/acetone, NaOH/EtOH/HCl and NaOH/H2O/HCl, pyridine/NaOH H2O/HCl, Et3N/dioxane/H2O/HCl, reflux at higher temperature, ethyl thiophosphate and aldehyde with thiourea in phosphoric acid, benzyl with thiourea in NaOH/EtOH, dimethylformamide (DMF)–K2CO3, and KOH/dimethylsulfoxide (DMSO), as well as with amino acid esters in the presence of CH2Cl2/Et3N, aqueous pyridine/Et3N/dioxane, KOH/H2O/HCl, NaHCO3/EtOH/HCl, AcOH/HCl, alkaline Al2O3, and DMF-H2O. Also, multiple-step procedures were reported including benzaldehydes, glycine, and thiocyanate, bromoacetyl bromide, sodium azide, amine, and CS2, vinyliminophosphorane with CS2, amine α-amino esters, nitrostyrenes, aromatic isothiocyanates, and MeOH/H2SO4/PTSA.
However, these methodologies usually involve several steps that inevitably lead to decrease in the quantitative yield of the reaction.

Water and aqueous-based solvent systems may represent an increasingly significant choice for the replacement of traditional solvents in synthetic chemistry. Aqueous solutions have potential advantages over the use of volatile organic compounds, and chemistry should occur at room temperature. Therefore, there is a need for the development of more gentle methods. In persistence of our work in organic synthetic methods, we herein describe a simple and mild method for the synthesis of thiohydantoins from S-amino acids and phenylisothiocyanate in triethylamine by using mixture of DMF and water as solvent.

RESULTS AND DISCUSSION

A literature survey revealed that the lower yields and longer reaction times were observed with different bases and solvents for the synthesis of PTH-thiohydantoins (Table 1). Subsequently, our initial approach for the preparation of 3,5-diphenyl-2-thioxoimidazolidin-4-one involved the condensation of S-amino acid with phenylisothiocyanate in the presence of an organic base and solvents such as water, ethanol, and dimethylformamide (DMF) at room temperature. The screening of literature reports and our optimizations revealed that Et$_3$N/aqueous DMF was the most efficient reaction condition for the transformation (Table 1, entry 8). However, by our optimization base-catalyzed reactions in aqueous ethanol gave modest yields with elongated reaction times (Table 1, entries 6 and 7) while in aqueous DMF about 98% yield was obtained (Table 1, entry 8). Thereafter, we studied effect of the selected cosolvent on time and yields of the product. It appeared that reaction time is lengthened and also there is a slight difference in yields in water and DMF when used separately. In cosolvent the reaction time decreased with increasing yields (Table 2). The quantitative yield was obtained in DMF/H$_2$O with a ratio 8:2 with a decrease in reaction time (Table 2, entry 6). Remarkably, the influence of the solvent DMF/H$_2$O has been investigated, resulting in a yield improvement. To examine the versatility of the protocol, we used phenylisothiocyanate to react with the structurally diverse S-amino acids under optimized reaction conditions and satisfactory results were achieved, ranging from 88% to 98% yields (Table 3, entries 1–16).

Table 1. Comparison for preparation methods of 5-alkyl/aryl-3-phenyl-2-thioxoimidazolidin-4-one

| Entry | Base     | Reaction conditions          | Time (h) | Yield (%) |
|-------|----------|-----------------------------|----------|-----------|
| 1.    | KOH      | EtOH, reflux, HCl           | 2        | 50\textsuperscript{[14]} |
| 2.    | Na$_2$CO$_3$ | Dioxane, reflux, HCl       | 4        | 80\textsuperscript{[16]} |
| 3.    | Ionic liquid | TFA/dry ACN, Na$_2$CO$_3$, rt | 8        | 77\textsuperscript{[17]} |
| 4.    | NaOH     | H$_2$O/acetone, reflux      | 2        | 60\textsuperscript{[18]} |
| 5.    | Et$_3$N  | CH$_2$Cl$_2$, reflux, HCl  | 2        | 52\textsuperscript{[20]} |
| 6.    | Et$_3$N  | 1:1 EtOH + H$_2$O, rt, HCl | 9        | 87        |
| 7.    | NaHCO$_3$  | 1:1 EtOH + H$_2$O, rt, HCl | 9.5      | 85        |
| 8.    | Et$_3$N  | DMF/H$_2$O, rt, HCl        | 1.5      | 98 (present work) |
To explore the scope of the reactions, we extracted the procedure to S-amino acids such as glycine, phenyl glycine, alanine, valine, leucine, serine, cysteine, asparagine, aspartic acid, lysine, proline, methionine, phenylalanine, glutamic acid, glutamine, and threonine. When the reaction was carried out in DMF and water in the presence of triethyl amine, the rate of reaction is noticeably increased and significant improvement in the yield was observed at room temperature. It has been found that the reaction smoothly proceeds with phenylisothiocyanate and various S-amino acids (Scheme 1), forming the five-membered functionalized 5-aryl/alkyl-3-phenyl-2-thioxoimidazolidin-4-ones. It should be noteworthy that no racemization at the 5-positions of 2-thiohydantoins is observed under the given reaction conditions. This was confirmed by the analysis of the $^1$H NMR spectra of the 2-thiohydantoins.[23a]

We obtained satisfactory results under optimized conditions with structurally diverse S-amino acids and phenylisothiocyanate (Table 3, entries 1–16). 2-Thiohydantoins resulting from amino acids with nonpolar side chains such as glycine, alanine, valine, leucine, phenylglycine, phenylalanine, and methionine, as well as polar side chains such as serine, cysteine, aspartic acid, asparagine, glutamine, and lysine, can be isolated simply by precipitation after acidification by 1 N HCl in up to 98% yields (Table 3). The corresponding 2-thiohydantoins arising from glutamic acid was not precipitated under our reaction conditions but hence derived by extraction with EtOAc after adding 1 N HCl (Table 3, entry 11), while PTH-proline was isolated without acidifying the reaction mixture after completion of reaction. On addition of HCl, the thiohydantoin ring was opened, which was confirmed by $^1$H NMR (Table 3, entry 13). It was isolated by addition of water and extraction in

| Entry | Reaction conditions | Time (h) | Yield (%) |
|-------|---------------------|----------|-----------|
| 1.    | H$_2$O              | 9        | 90        |
| 2.    | 8:2 H$_2$O/DMF      | 5        | 91        |
| 3.    | 6:4 H$_2$O/DMF      | 3.5      | 92        |
| 4.    | 5:5 H$_2$O/DMF      | 3        | 92        |
| 5.    | 4:6 H$_2$O/DMF      | 2        | 93        |
| 6.    | 2:8 H$_2$O/DMF      | 1.5      | 98        |
| 7.    | 1:9 H$_2$O/DMF      | 7        | 89        |
| 8.    | DMF                 | 7.5      | 84        |

*Reaction conditions: 02 mmol phenylisothiocyanate, 02 mmol S-phenylglycine, Et$_3$N, and 10 mL solvent, stir, rt.*
Table 3. Synthesis of PTH–amino acid*

| Entry | Substrate | Product | Reaction time (h) | Yield (%) |
|-------|-----------|---------|-------------------|-----------|
| 1     |           |         | 2                 | 95        |
| 2     |           |         | 1.5               | 92        |
| 3     |           |         | 2.5               | 97        |
| 4     |           |         | 3                 | 97        |
| 5     |           |         | 1.5               | 98        |

* R - alkyl, aryl, benzyl

16 examples up to 98% yield
| Entry | Substrate | Product | Reaction time (h) | Yield (%) |
|-------|-----------|---------|-------------------|-----------|
| 6     | HO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>(CH)<sub>2</sub>NH<sub>2</sub> | S<sub>2</sub>N<sub>2</sub>CH<sub>2</sub>(CH)<sub>2</sub>NH(C<sub>6</sub>H<sub>4</sub>) | 6       | 96        |
| 7     | HO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>(CH)<sub>2</sub>NH<sub>2</sub> | S<sub>2</sub>N<sub>2</sub>CH<sub>2</sub>(CH)<sub>2</sub>NH(C<sub>6</sub>H<sub>4</sub>)OH | 3       | 96        |
| 8     | HO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>(CH)<sub>2</sub>NH<sub>2</sub> | S<sub>2</sub>N<sub>2</sub>CH<sub>2</sub>(CH)<sub>2</sub>NH(C<sub>6</sub>H<sub>4</sub>)SH | 5       | 88<sup>b</sup><sup>c</sup> |
| 9     | HO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>(CH)<sub>2</sub>NH<sub>2</sub> | S<sub>2</sub>N<sub>2</sub>CH<sub>2</sub>(CH)<sub>2</sub>NH(C<sub>6</sub>H<sub>4</sub>)CO | 6       | 95        |
| 10    | HO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>(CH)<sub>2</sub>NH<sub>2</sub> | S<sub>2</sub>N<sub>2</sub>CH<sub>2</sub>(CH)<sub>2</sub>NH(C<sub>6</sub>H<sub>4</sub>)CO<sub>2</sub>NH | 5       | 91        |
| 11    | HO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>(CH)<sub>2</sub>NH<sub>2</sub> | S<sub>2</sub>N<sub>2</sub>CH<sub>2</sub>(CH)<sub>2</sub>NH(C<sub>6</sub>H<sub>4</sub>)CO | 5.5     | 96<sup>b</sup> |
| 12    | HO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>(CH)<sub>2</sub>NH<sub>2</sub> | S<sub>2</sub>N<sub>2</sub>CH<sub>2</sub>(CH)<sub>2</sub>NH(C<sub>6</sub>H<sub>4</sub>)CO | 3       | 95        |

(Continued)
EtOAc with good yield. Amino acid–thiohydantoin was achieved in 1–6 h for completion with quantitative yields (Table 3, entries 1–16).

**Table 3.** Continued

| Entry | Substrate | Product | Reaction time (h) | Yield (%) |
|-------|-----------|---------|-------------------|-----------|
| 13    |           |         | 1.5               | 90\(^b\)  |
| 14    |           |         | 1.5               | 97        |
| 15    |           |         | 6                 | 95        |
| 16    |           |         | 6                 | 93\(^c\)  |

\(^a\)Reaction conditions: \(S\)-amino acid (02 mmol), phenylisothiocyanate (02 mmol), \(Et_3N\) (02 mmol), and 8:2 DMF/H\(2O\) (10 mL), stir, rt.

\(^b\)EtOAc for extraction of product.

\(^c\)\(Et_3N\) (04 mmol).

**Scheme 1.** Synthesis of PTH-amino acid from \(S\)-amino acids and phenylisothiocyanate.
CONCLUSION

In conclusion, we developed an effective method for the synthesis of thiohydantoins from the reaction of S-aminoo acid with phenylisothiocyanate by using triethylamine in DMF-H$_2$O at room temperature, which affords pure products in excellent yields. The advantages of this procedure include mild reaction conditions, broad application scope, good yields, and simple workup process.

EXPERIMENTAL

To a solution of amino acid (0.2 mmol) with TEA in (8:2) DMF and water (10 mL), phenylisothiocyanate (0.2 mmol) was added. The reaction mixture was stirred at room temperature. The progress of reaction was monitored by thin-layer chromatography (TLC; 30% EtOAc/hexane or 5–10% MeOH/CHCl$_3$). The solid product was obtained after acidification with 1 N HCl. The product was filtered and recrystallized with aqueous EtOH to afford pure products.

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SUPPLEMENTAL MATERIAL

Supplementary material includes experimental details, characterization data of all compounds, and FT-IR, $^1$H NMR, $^{13}$C NMR, and mass spectra for this work, which can be accessed on the publisher’s website.

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