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Synthesis and Characterization of Amino Acid-Derived Hydantoins

Ee-Zhen Chin[1], Siow-Ping Tan[1,*], Sook-Yee Liew[2] and Thomas Kurz[3]
[1]Department of Physical Science, Faculty of Applied Sciences,
Tunku Abdul Rahman University College, 53300 Kuala Lumpur, Malaysia
[2]Chemistry Division, Centre for Foundation Studies in Science,
University of Malaya, 50603 Kuala Lumpur. Malaysia
[3]Institute of Pharmaceutical and Medicinal Chemistry, Heinrich-Heine Universität Düsseldorf,
Universitätsstr. 1, 40225 Düsseldorf, Germany
*Corresponding author (e-mail: tansp@tarc.edu.my)

The Urech hydantoin synthesis is the chemical reaction of amino acids with potassium cyanate and hydrochloric acid, which allows access to hydantoins and its derivatives. Most of them are biologically active with varieties of structural diversity that make them synthetically attractive. A series of hydantoins were synthesized from various α-amino acids in a reaction with hydrochloric acid and ethanol as the first step, and with potassium cyanate as the second step for the formation of ureido derivatives. Lastly, the cyclization of ureido derivatives yielded the desired hydantoin products. All hydantoins were obtained in a good yield and fully characterized by NMR and IR spectroscopy. This strategy provides a variety of biologically significant hydantoin derivatives.

Key words: Alanine; glycine; phenylalanine; hydantoins; Urech hydantoin synthesis

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Hydantoins (imidazolidine-2,4-diones) are important heterocyclic compounds in organic chemistry [1]. The significant biologically active properties of hydantoin derivatives make them an important structural component of various valuable pharmaceuticals, such as phenytoin as an antiepileptic [2,3], azimilide as an anti-arrhythmic [4], nitrofurantoin as an antibacterial agent [5], dantrium as a skeletal muscle relaxant [6], nilutamide as an orally active antiandrogen [7] and sorbinil as an orally active aldose reductase inhibitor [8] (Figure 1).

Over the past decade, tremendous efforts have been invested in synthesizing and studying these five-membered heterocycles [1]. There are various synthetic pathways for hydantoin; the three most common ones are the Urech or the Read synthesis, the Bucherer-Bergs reaction and the Biltz reaction [9]. The Bucherer-Bergs reaction [10] affords racemic hydantoins which are based on carbonyl or dicarbonyl condensation from carbonyl compounds, potassium or sodium cyanide and ammonium carbonate. The Biltz reaction [11] is historically known for its role in the synthesis of the antiepileptic drug, phenytoin from benzil and urea whereas the Urech or the Read synthesis [12] relates to the reaction between amino acid derivatives and isocyanates.

There have been many studies on the use of α-amino acids in the synthesis of substituted hydantoins including the cyclization of carbamate-protected amino amides [13], carbamate-protected dipeptides [14], or ureido derivatives of amino acids or amino esters [2,15]. However, the above-mentioned approaches involve the use of protecting groups which results in lower yields. Protecting groups that are available presently may require harsh conditions, specialized equipment, or expensive or air/moisture-sensitive reagents [16].

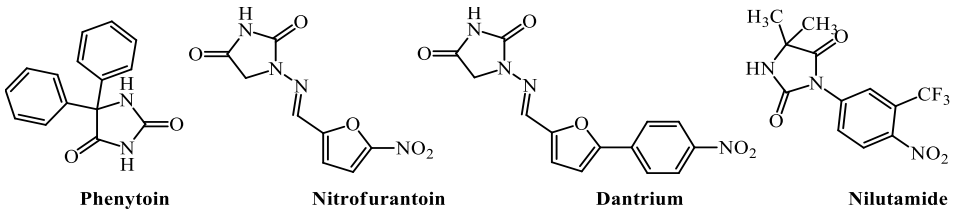

Figure 1. Examples of substituted hydantoins with various biological activities

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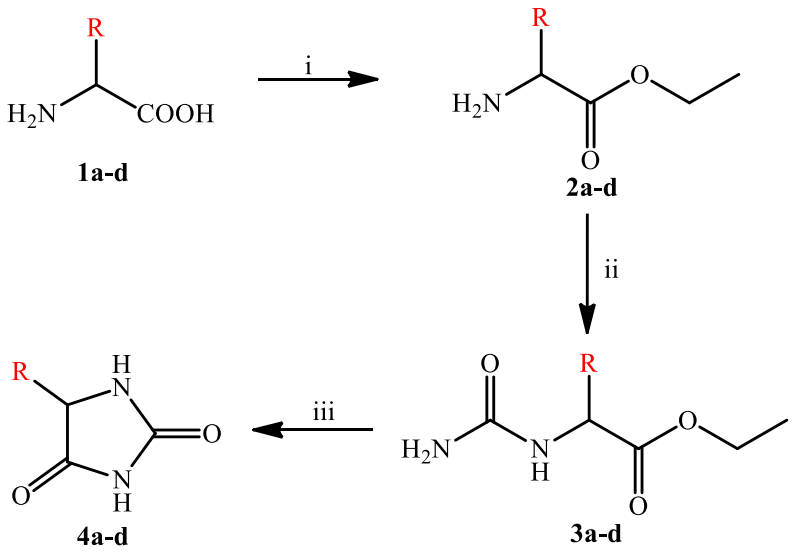


Scheme 1. Synthesis and reactivity of ethyl ester hydrochloride **(2a-d)**, ureido derivatives **(3a-d)**, Hydantoin derivatives **(4a-d)**. Reagents: (i) HCl gas and EtOH, overnight; (ii) KCNO, 2h, –5°C; (iii) 37% v/v HCl, overnight

In our continuing search for novel and effective methods for the preparation of various organic molecules, we were prompted to seek a mild and efficient condition for the synthesis of hydantoin and its derivatives. To improve the existing methodologies and increase the yields of the product, we herein describe a simple, efficient, and inexpensive procedure for the Urech Hydantoin synthesis under refluxing conditions with good to excellent yields. In this study, α-amino acids used in the Urech Hydantoin synthesis are glycine, alanine, phenylalanine and methionine.

MATERIALS AND METHODS

The synthesis and reactivity of hydantoin derivatives are summarized in Scheme 1. All chemicals and reagents used in the synthesis were of analytical grade and procured from Sigma-Aldrich and Merck. The solvents for the synthesis of the compounds were used without further purification. For the preparation of hydrogen chloride gas, concentrated sulphuric acid (94%–96%) was added dropwise to sodium chloride in a molar ratio of 2:1. The hydrogen chloride gas was released into water. The pH of the water was recorded with a pH meter to monitor the reaction. For the preparation of potassium cyanate, urea was ground together with potassium carbonate with a pestle and mortar. The solid mixture was heated slowly on the crucible and the flame was slowly increased. When the solid partially melted, gases were released. Urea was added in excess to make sure all the potassium carbonate was fully utilized in the reaction.

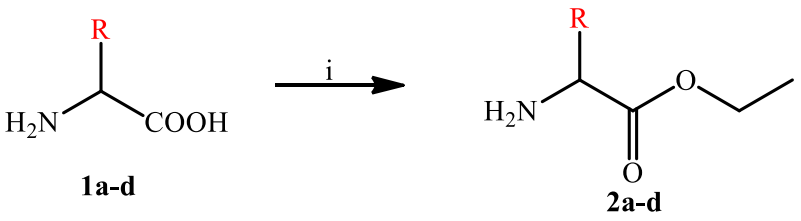
Instrument

The chemical structures of all the compounds were confirmed by FT-IR as well as ^{1}H and ^{13}C NMR spectroscopy. FT-IR spectra were recorded on an FT-IR Spectrometer (Perkin-Elmer spectrum 100) in the IR region of (600–4000 cm^{-1}) using Attenuated Total Reflection (ATR) techniques. NMR spectra were recorded on a JOEL 500 MHz Spectrometer using tetramethylsilane as an internal standard and deuterated dimethyl sulfoxide (DMSO-d_6) as the solvent. The melting point was determined with a Stuart SMP 20 Melting Point apparatus.

Synthesis

Synthesis of hydantoin ethyl ester hydrochloride

A series of amino acids **(1a-d)** (5 g) was added dropwise and covered with absolute ethanol (15 mL) while suspended in an oil bath. After stirring for 10 min, hydrogen chloride gas was bubbled through the mixture. The amino acid was slowly dissolved in 30 minutes. Ethanol was continuously added to replace the evaporated ethanol. The mixture was treated with hydrogen chloride gas for an additional 15 minutes ensures the reaction was complete. The hydantoin ethyl ester hydrochloride **2a-d** was occasionally crystallized during this period. The reaction mixture was cautiously evaporated to dryness at 45–50 °C overnight to give **2a-d** as a solid product (Scheme 2).



Scheme 2. Synthesis of hydantoin ethyl ester hydrochloride

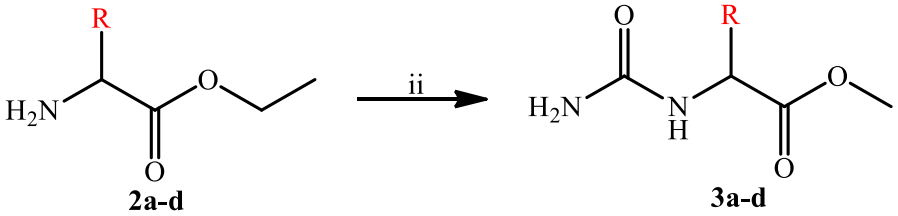
Table 1. Optimization of the esterification conditions

Entry	Compound	R	Conditions	Temperature (°C)	Yield %
1	2a	H	3M HCl	65	No reaction.
2	2a	H	HCl gas	65	74%
3	2b	CH_3	HCl gas	80	93%
4	2c	Benzene	HCl gas	80	-*
5	2d	$C_2H_4SHCH_3$	HCl gas	80	-*

* Product in liquid form.

Synthesis of Ureido derivatives

The ethyl ester hydrochloride **(2a-d)** (0.875 g/mL) was added to a freshly prepared potassium cyanate solution (0.5 g/mL). The reaction mixture was stirred until precipitation occurred (4–5 min) and then cooled for 2 hours in a –5 °C ice bath. The solid product **(3a-d)** formed was filtered and air-dried in a fume hood (Scheme 3).

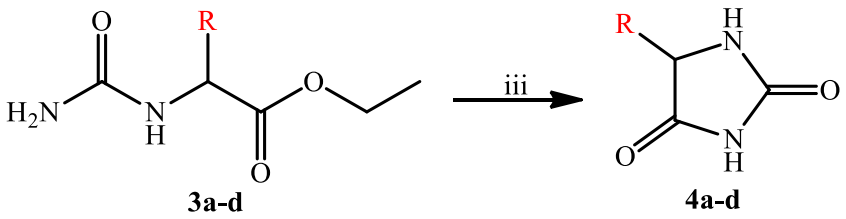


Scheme 3. Synthesis of ureido derivatives

Table 2. Optimization of the Urech synthesis conditions

Entry	Compound	R	Duration (hr)	Temperature (°C)	Yield %
1	3a	H	2	-5	>99
2	3a	H	6	-5	>99
3	3a	H	6	25	51.58
4	3b	CH_3	24	-5	-*
5	3c	Benzene	2	-5	>99
6	3d	$C_2H_4SHCH_3$	2	-5	-*

* Product in liquid form.



Scheme 4. Synthesis of hydantoin ring

Table 3. Optimization of the acid-cyclization conditions

Entry	Compound	R	Duration (hr)	Condition	Yield %
1	4a	H	24	25% w/w HCl	80%
2	4a	H	24	25% v/v HCl	81%
3	4a	H	24	10% v/v HCl	91%
4	4a	H	24	37% v/v HCl	93%
5	4a	H	72	25% v/v H_2SO_4	-
6	4a	H	72	50% v/v H_2SO_4	-
7	4a	H	72	96% v/v H_2SO_4	-
8	4b	CH_3	24	37% v/v HCl	>99%
9	4c	Phenyl	24	37% v/v HCl	79%
10	4d	$C_2H_4SHCH_3$	24	37% v/v HCl	>99%

Synthesis hydantoin derivatives

The ureido derivative **3a-d** was added and wetted with 10 mL of hydrochloride acid. The mixture was evaporated to dryness on a steam bath overnight (Scheme 4).

Spectral data of the hydantoin derivatives

Hydantoin **(4a)**

Colourless crystals (93%). Mp 214-216°C; IR (KBr): *v*= 3363 (N–H), 1717 (C=O) 1203 (C–N), 721 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6), δ (ppm): 3.84 (d, J = 0.5 Hz, 2H), 7.70 (br s, H), 10.60 (br s, H); ^{13}C NMR (DMSO-d_6), δ (ppm): 47.4, 158.5, 174.0.

5-Methylhydantoin **(4b)**

Colourless crystals (>99%). Mp 76-78°C; IR (KBr): *v*= 3310 (N-H), 1713 (C=O), 1428 (C–H), 1043 (C–N), 739 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6), δ (ppm): 1.19 (d, J = 5.5 Hz, 3H), 4.00 (dd, J = 12.0 Hz, 6.0Hz, H), 7.87 (br s, H), 10.57 (br s, H); ^{13}C NMR (DMSO-d_6), δ (ppm): 17.4, 53.5, 157.4, 177.1.

5-Phenylhydantoin **(4c)**

Colourless crystals (79%). Mp 173-175°C; IR (KBr): *v*= 3056 (N–H), 2768 (C–H), 1728 (C=O), 1604 (C=C), 1416 (OH), 1185 (C–N), 746 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6), δ (ppm): 4.31 (t, J = 12.0 Hz, H), 7.18 (d, J = 9.0 Hz, H), 7.25 (dd, J = 6.0 Hz, 5.0 Hz, H), 7.27 (s, H), 7.89 (br s, H), 10.40 (br s, H); ^{13}C NMR (DMSO-d_6), δ (ppm): 58.4, 126.6, 128.1, 128.6, 129.7, 129.5, 135.6, 157.1, 175.2.

5-(2-(Methylthio)ethyl)hydantoin **(4d)**

Colourless crystals (>99%). Mp 74-76°C; IR (KBr): *v*= 3146 (N–H), 2762 (S–H), 1725 (C=O), 1420(C–H), 1179 (C–N), 747 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d_6), δ (ppm): 1.67–1.69 (m, 2H), 1.97 (s, 3H), 2.45–2.48 (m, 2H), 4.02 (dd, J = 7.5 Hz, 4.5Hz, H), 7.98 (br s, H), 10.60 (br s, H); ^{13}C NMR (DMSO-d_6), δ (ppm): 15.0, 29.3, 31.5, 57.0, 157.9, 176.4.

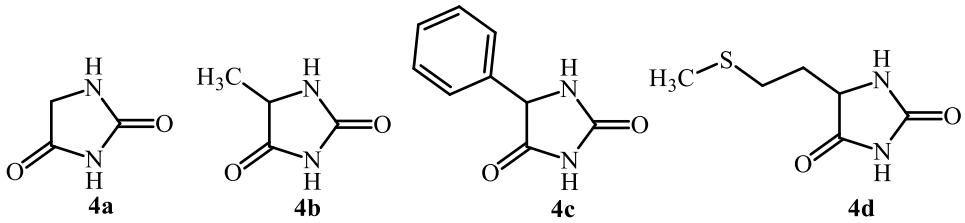


Figure 2. Synthesized hydantoin derivatives **4a-d**

RESULTS AND DISCUSSION

Glycine **1a** was treated with ethanol in excess and hydrogen chloride gas to start the reaction which produced the resulting esters. In this reaction, hydrogen chloride gas acted as a catalyst in the formation of the cation. The resulting cation was then protonated to give a delocalized carbocation, a better electrophile to attack the hydroxy group of the ethanol. By eliminating water, glycine ethyl ester hydrochloride **2a** was formed with 74% yield from the esterification process. In this reaction, heat was applied to facilitate the reaction process. Our initial concept of using hydrochloric acid as the catalyst (Table 1, Entry 1) was not successful due to the presence of hydroxonium ion, H_3O^+ which acted as a catalyst in this case and led to hydrolysis rather than esterification. Thus, all the remaining syntheses of compounds **2a-d** used hydrogen chloride gas. However, the reactions for alanine **1b**, phenylalanine **1c**, and methionine **1d** were conducted at higher temperatures because their structures are more complex and thus require more heat to overcome their high activation energies.

Compound **2a** was used for the next step without further purification. Synthesis of ureido derivatives of compound **2a** in the presence of potassium cyanate at refluxing temperature gave an excellent yield (>99%) of compound **3a** as colourless crystals with. In this reaction, the *N*-terminal moiety of compound **2a** was activated by the addition of amine. To ensure high yields, reaction conditions were optimized by varying the temperature, conditions, and reaction times. The results obtained are summarized in Table 2. Similar procedures were repeated for compounds **3b**, **3c** and **3d**. For compounds **3b** and **3d**, there were no precipitates produced during the synthesis.

In the next step, hydantoin **4a** (93% yield) was synthesized from compound **3a** using acid-cyclization in the presence of hydrochloric acid on a steam bath. In this step, the conditions were varied by using different concentrations and types of acid. From Table 3, 37% v/v HCl gave the best yield whereas no cyclization occurred when sulphuric acid was used as the acid catalyst. Therefore, synthesis of the other three compounds **3b**, **3c** and **3d**,was also performed using 37% v/v HCl and resulted in good to excellent yields.

From the FTIR analysis, the presence of the signature IR bands gave significant evidence of the formation of hydantoin and its derivatives (Figure 2). A strong band at 1705–1725 cm^{-1} was assigned to the *v*(C=O) stretch of the cyclopentenone linkage which indicates the formation of a ring [17]. This was further corroborated by the presence of *v*(–NH) stretching in the range of 3310–3350 cm^{-1}, indicating the presence of amines in the ring. The sharp bands in the range of 720–755 cm^{-1} were due to the aromatic *v*(C=C). In addition, a *v*(C=N) medium intensity stretching band was observed in the region of 1020–1250 cm^{-1} indicating the linkage between carbon and amine in the aromatic ring. For **4b**, a medium intensity bend *v*(C–H) was observed in the region of 1425–1450 cm^{-1} due to the presence of a methyl group. A stretching bend was observed for **4c** at 1566–1650 cm^{-1} which represented the benzene ring *v*(C=C) on the phenylalanine. In the spectrum for **4d**, there was a weak band observed in the range of 2550–2800 cm^{-1} indicating the presence of S–H stretching.

In the ^{1}H NMR of **4a**, the signal at 3.84 ppm corresponds to the methylene groups (–CH_2–) on the hydantoin ring, whereas, the presence of two broad single peaks at 7.70 ppm and 10.60 ppm indicate the presence of –NH protons, signifying the amines on hydantoin rings [2]. In the ^{13}C NMR spectrum of **4a**, there are three carbon signals at 47.4, 158.5 and 174.0 ppm which represent the aromatic carbon (–CH_2–) and two carbonyl groups (–C=O) on the ring. A doublet at 1.19 ppm can be observed in the ^{1}H NMR spectrum of **4b** that corresponds to the methyl group CH_3 attached to the ring. Two broad single peaks, at 7.87 and 10.57 ppm, represent the –NH proton for **4b** which are also present in the ^{1}H NMR of **4a**. In addition, a proton (–CH) signal at C-5 shows a doublet of doublets peak at 4.0 ppm for **4b**. The ^{13}C NMR spectrum of **4b** has four signals at

17.4 (–CH_3), 53.5 (–CH), 157.4 (–C=O) and 177.1ppm (–C=O) respectively.

The ^{1}H NMR spectrum of **4c** shows triplet peaks at 4.31 ppm, corresponding to proton (–CH) at 5-substituted carbon bonded to a benzene ring. The three peaks observed at 7.18, 7.25 and 7.27 ppm correspond to the protons on the benzene ring. The presence of –NH protons on the rings is confirmed by two broad single peaks at 7.89 ppm and 10.40 ppm. In the ^{13}C NMR spectrum of **4c**, there are nine signals observed where, 58.4 ppm represents carbon (–CH) at the 5-substituted position, while 126.6, 128.1, 128.6, 129.7, 129.5, and 135.6 ppm represent carbons (C=C) on the benzene rings, and finally 157.1 and 175.2 ppm represent the carbonyl carbons (–C=O). For compound **4d**, two multiplets were recorded at 1.67-1.69 ppm and 2.45-2.48 ppm, corresponding to the methylene groups (–CH_2). The peak at 1.97 ppm represents the proton of methyl group (–CH_3) at the terminal of the substituted chain, whereas the one at 4.02 ppm represents the proton on the 5-substituted carbon (–CH). Two single broad peaks corresponding to (–NH) protons were observed at 7.98 and 10.60 ppm. There are six signals in the ^{13}C NMR of **4d:** 15.0, indicating the methyl group (–CH_3), 29.3 and 31.5 indicating the methylene group (–CH_2), 57.0 (–CH), and, 157.9 and 176.4 ppm corresponding to the carbonyl group (C=O).

In previous studies on the synthesis of hydantoin derivatives using α-amino acids, toxic protecting groups such as *tert*-butoxycarbonyl (Boc), acid-sensitive *tert*-butyl ester, *tert*-butyl ether, silyl and carboxybenzyl (Cbz), were used. Pan and co-workers also reported the use of a catalyst, such as Tf_2O, for the synthesis of hydantoin derivatives. These reactions were performed at low reaction temperatures (–78 to 25°C) to obtain a better yield [9]. More recently, Waser *et al*. were able to obtain 1,5-substituted enantiopure hydantoins from amino acid in the presence of a hypervalent iodine cyanation reagent (cyanobenziodoxolone, CBX) which is a potentially hazardous compound [1]., Although multistep reactions were involved in our study, only simple reagents were used, such as α-amino acids and hydrogen chloride gas as a catalyst at moderate reaction temperatures (–5 to 25 °C) to obtain an encouraging yield of the desired products.

CONCLUSION

In conclusion, an efficient and practical method for the synthesis of hydantoins and its derivatives has been developed. The synthesis began with the esterification of α-amino acid with ethanol and hydrogen chloride gas; then continued with potassium cyanate; and lastly acid-cyclization with hydrochloric acid which gave a good to excellent yield for the reaction. The method is expected to be highly useful in synthetic and medicinal chemistry.

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