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Chemical Synthesis Strategies for Thiohydantoin Derivatives: A Comprehensive Review

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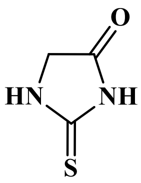
Abstract: The synthesis of 2-thiohydantoin derivatives has been explored through both classical and modern methodologies. In this sulfur-containing analog of hydantoin, one or both carbonyl groups are substituted with thiocarbonyl moieties. This study reviews a broad spectrum of synthetic approaches, including traditional methods such as theorema and reactions involving amino acids, as well as advanced techniques like microwave-assisted synthesis. Furthermore, various reaction mechanisms and the resulting thiohydantoin derivatives are thoroughly illustrated.

Keywords: 2-thiohydantoin, Synthesis strategies, Chemical reactions.

1. Introduction

Thiohydantoin is a vital chemical compound due to its potential applications in both industrial and medical fields. These compounds can be synthesized through various methods, ranging from traditional approaches, such as reactions involving thiourea and amino acids, to more modern techniques utilizing advanced technologies, including microwave-enhanced reactions. This review aims to examine the various methods used for synthesizing 2-thiohydantoin derivatives and to provide a comprehensive evaluation of their efficiency and mechanisms of action [1,2].

Our goal is to highlight recent progress in the field and the challenges researchers encounter by examining the current literature. This review primarily focuses on the synthetic methods employed to produce 2-thiohydantoin derivatives, showcasing both conventional and innovative techniques. Thiohydantoin, a sulfur (S, or thio) analog of hydantoin, is formed when one or two carbonyl groups are replaced with thiocarbonyl groups [3,4]. Three thiohydantoins are present: -2-thiohydantoin **(1)**, 4-thiohydantoin **(2)**, and 2,4-thiohydantoin **(3)**.



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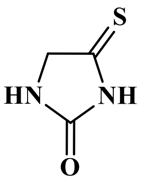

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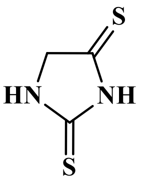

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2. Synthesis of 2-Thiohydantoin Derivatives

The synthesis of 2-thiohydantoins can be categorized based on the starting materials. The following sections provide a detailed overview, complemented by a critical analysis of each approach.

2.1 Synthesis from Amines and Isothiocyanates

This route is a cornerstone in thiohydantoin synthesis, offering direct access through the reactivity of the isothiocyanate group.

2.1.1 From Amino Cyanides and Isothiocyanates

The reaction between an amino cyanide (6) and an

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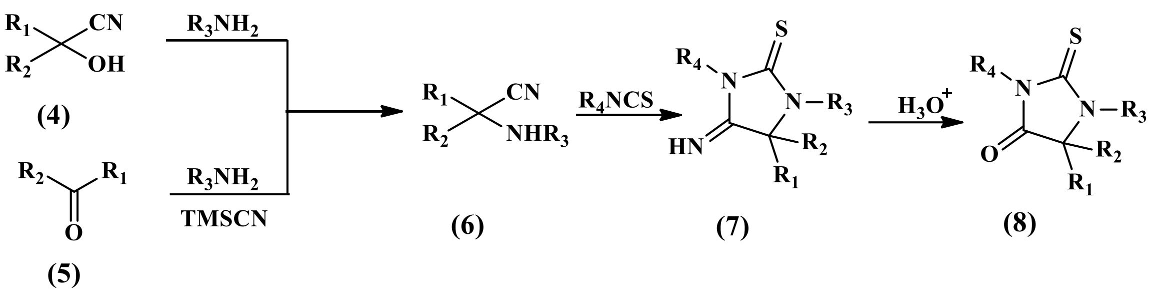
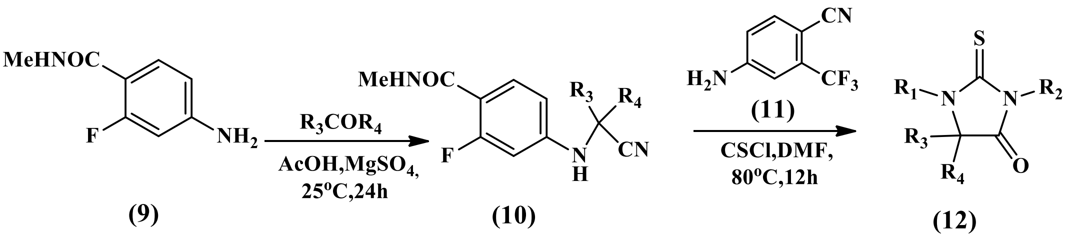
isothiocyanate yields a thiohydantoin-4-imine intermediate (7). Subsequent mild acid hydrolysis provides the 2-thiohydantoin derivative (8) (Scheme 1). Cyan amine was synthesized either by treating cyanohydrin (4) with an amine or by reacting ketone (5) with an amine [5] in the presence of trimethylsilyl cyanide [6,7], as also discussed by Gupta et al. (2025) [8].



Scheme 1. Synthetic procedure for 2-thiohydantoins from amino cyanide.

2.1.2 From Amides

A more specialized route involves the fluoro-substituted benzamide 4-amino-2-fluoro-N-methyl-benzamide (9), which reacts with a range of ketones and trimethylsilyl cyanide (TMSCN) to afford adduct (10). This intermediate is then treated sequentially with an aromatic amine, such as 4-amino-2-(trifluoromethyl)benzonitrile (11), and thiophosgene, leading to cyclization and the formation of 2-thiohydantoins (12) (Scheme 2) [9,10]. While this approach is practical, the use of thiophosgene necessitates careful handling due to its toxicity, which may limit the method's scalability.



R1= 6-Cyano -5 -trifluoromethylphenyl

R2= 3-Fluoro -4 -(methylcarbamoyl)phenyl,3-fluoro -4 -(methoxycarbonyl)phenyl,4-carboxy -3 -fluorophenyl,4-carbamoyl -3 -fluorophenyl.

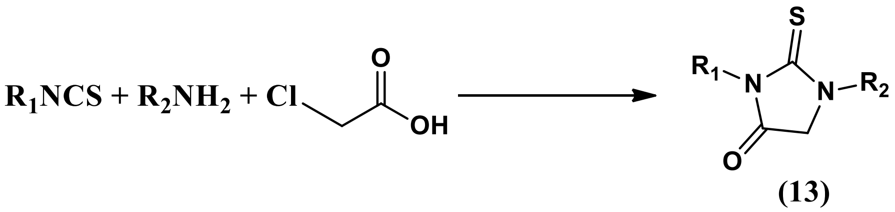
R3= H,Me,MeOCH2.

R4= Me,H,MeOCH2,PhCH2OCH2,EtO2CCH2,HOCH2,MeOCH2.

Scheme 2. Synthesis of 2-thiohydantoins **(12)**.

2.1.3 One-Pot Synthesis from Amines

A significant advancement in terms of efficiency is the one-pot [11] (Scheme 3) three-component coupling of amines, ethyl chloroacetate, and isothiocyanates under solvent-free conditions, yielding thiohydantoins (13) (R1 = Ph, Me; R2 = alkyl, aryl) from easily accessible substrates. This approach aligns with green chemistry principles by eliminating organic solvents, reducing the number of reaction steps, and enhancing atom economy. It is particularly advantageous for high-throughput synthesis of diverse thiohydantoin libraries. In Table 1, you can find the comparative analysis of the synthesis of amines/isothiocyanates.



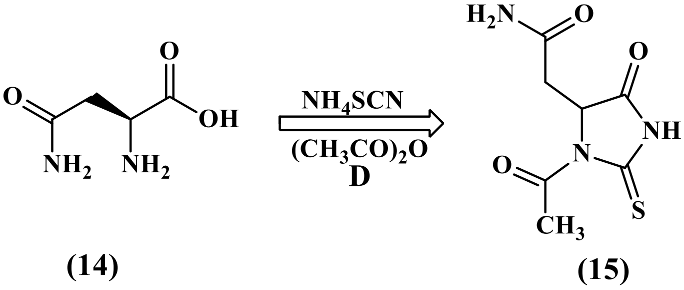
Scheme. 3 Synthesis of 2-thiohydantoins **(13)**.

Table 1. Comparative Analysis of Synthesis from Amines/Isothiocyanates.

Method	Key Reagents/Conditions	Typical Yield Range	Advantages	Limitations
Amino Cyanides (Sch. 1)	RNH_2, TMSCN, R'NCS, mild acid	Moderate-High	Modular, diverse substitution	Requires the preparation of amino cyanide
From Amides (Sch. 2)	Fluoro-benzamide, ketone, TMSCN, R'NCS, Thiophosgene	Moderate	Access to specific heteroaromatic systems	Uses toxic thiophosgene, multi-step
One-Pot (Sch. 3)	RNH_2, R'NCS, $ClCH_2COOEt$, solvent-free, Δ	High	Green, efficient, high atom economy, one-pot	May require optimization for each substrate

2.2 Synthesis from Amino Acid Derivatives

Classical methods often start from amino acids. For example, L-asparagine (14) reacts with ammonium thiocyanate in acetic anhydride to yield the racemic N-acetyl-2-thiohydantoin-asparagine derivative (15) [12-14] Scheme 4. This Edman-like degradation chemistry is robust but often yields racemic products, which is a significant drawback for medicinal chemistry applications.



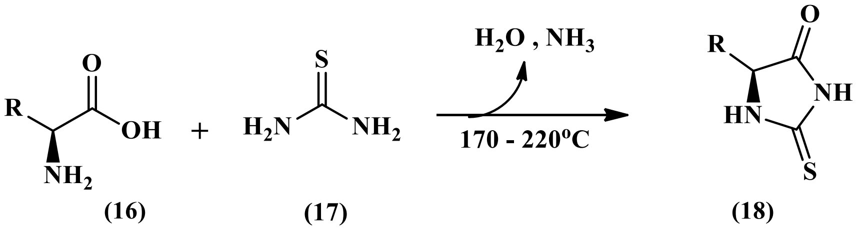
Scheme 4. Synthesis of rac-N-acety-2-thiohydantoin-asparagine. (15)

2.3 Synthesis from Thiourea Derivatives

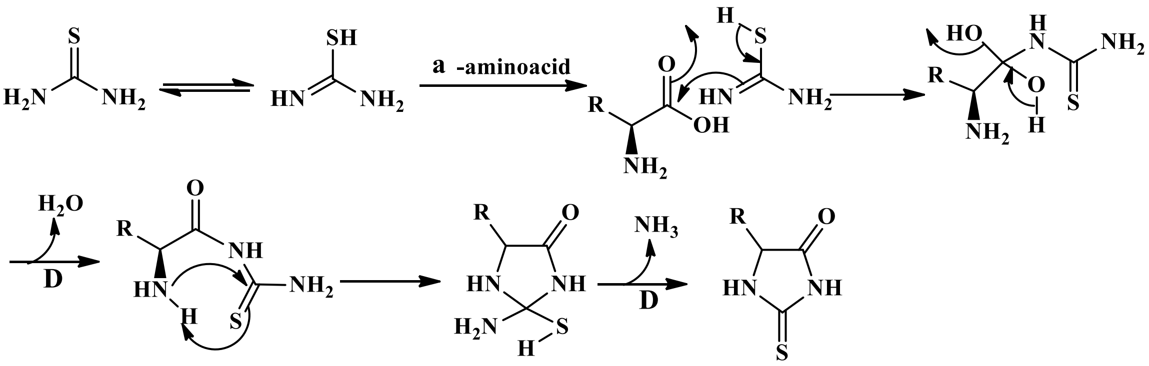
Thiourea and its derivatives are versatile and economical starting materials for the synthesis of thiohydantoin.

2.3.1- Thiourea with α-amino acid [15]

The reaction of an α-amino acid with thiourea is a classic method, proceeding via the initial formation of a thioureido acid intermediate (16/17) that cyclizes to the 2-thiohydantoin (18), as shown in Scheme 5. The mechanism involves dehydration and cyclization, as outlined in Scheme 6. This method is straightforward but can yield moderate results and generate stoichiometric waste [16].

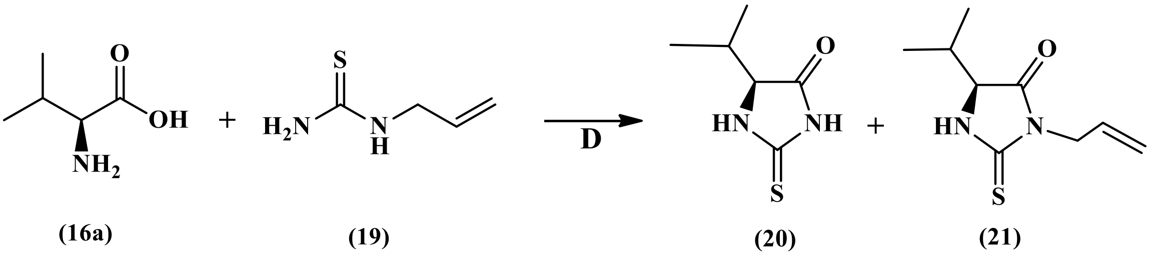


Scheme 5. The general preparation of 2-thiohydantoins from α-amino acids and thiourea (18) [16].



Scheme 6. The mechanism of 2-thiohydantoin formation.

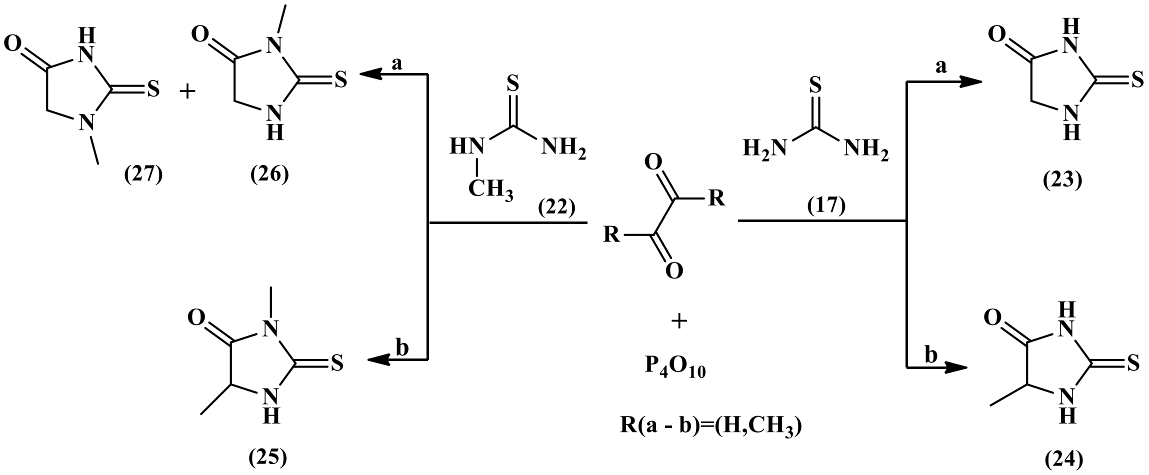
The reaction between L-valine and N-allylthiourea to form a mixture of products, including an intermediate thiohydantoin (Scheme 7).



Scheme 7. The reaction between L-valine and N-allylthiourea.

2.3.2- Thiourea with carbonyl compounds

A highly adaptable one-pot, three-component condensation between thiourea (17), aldehydes, and P_4O_{10} in aqueous medium efficiently yields 5-substituted thiohydantoins (23-27). This method is attractive due to its simplicity and use of water as a solvent, aligning with the goals of green chemistry. Recent modifications have focused on catalytic systems to enhance yields and reduce reaction time [17]. Synthesis of thiohydantoins (23-27) via a highly adaptable one-pot, three-component condensation reaction involving thiourea (17) and a carbonyl compound (Scheme 8).



Scheme 8. Synthesis of thiohydantoins **(23- 27)**.

2.3.3- Benzyl with urea or thiourea

The reaction of benzil (28) with urea (29) or thiourea(17) is a traditional route to 5,5-diphenylhydantoin (phenytoin, 30a) and its thio analog (30b) [18]. Modern improvements involve microwave irradiation, which drastically reduces reaction times and improves yields [19-21]. Scheme 9 compares the traditional (Method A) and microwave-assisted (Method B) approaches, with the latter offering a clear advantage in efficiency.

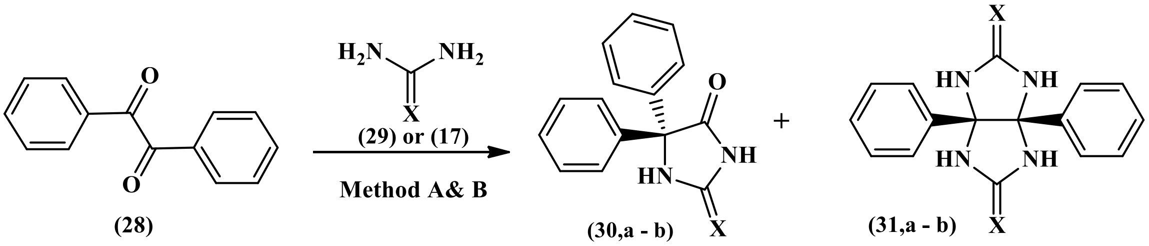
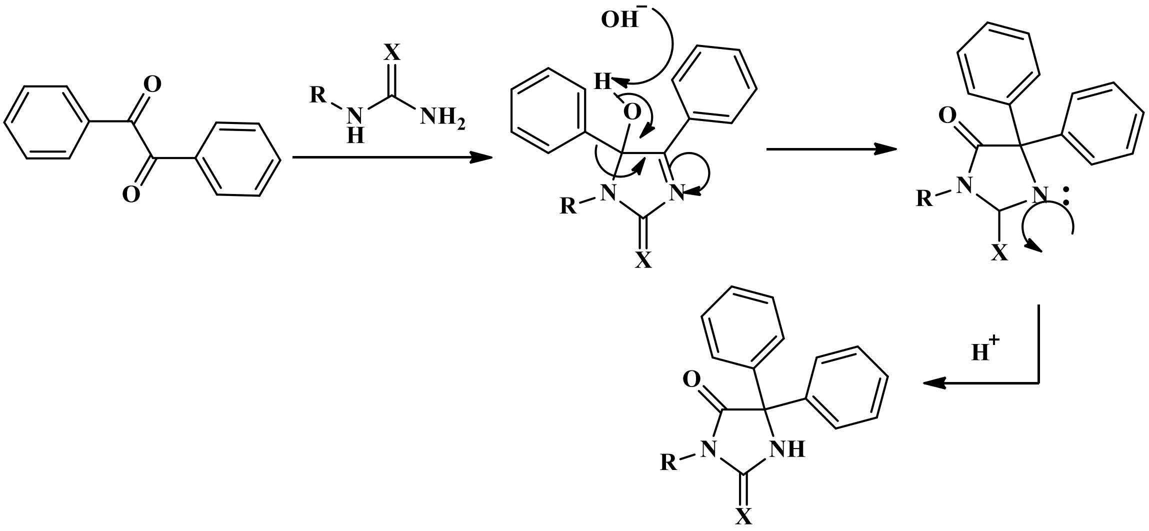


Diagram 10 explains. Proposed mechanism for condensation of benzyl and aquiloria followed by benzyl rearrangement [4].

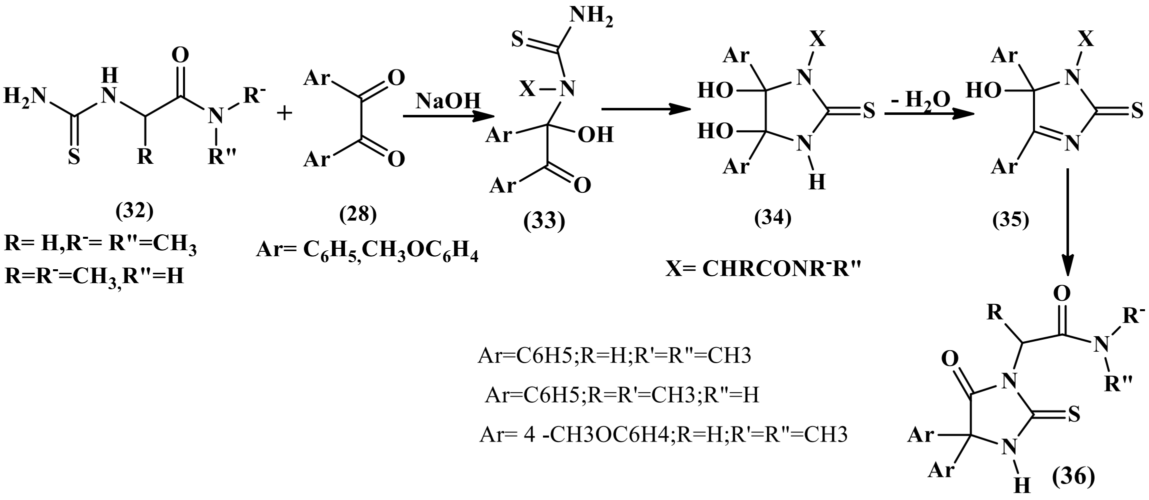
Scheme 9. Synthetic routes to diphenylhydantoin and diphenyl thiohydantoin. (31a-b)



Scheme 10. Proposed mechanism of condensation of benzyl and alkylurea, followed by the benzylic rearrangement [4].

2.3.4- Thioureido-acetamides with benzyl

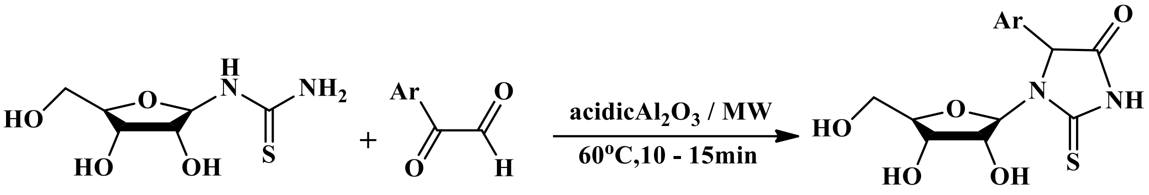
Thioureido-acetamides (32) and benzyl derivatives (28) interacted to generate 5,5-diaryl-thiohydantoins (36) when sodium hydroxide (NaOH) was present, as shown in Scheme 11.



Scheme 11. Synthesis of the 5,5-diaryl-thiohydantoins **(36)**.

2.4 Microwave-Assisted Synthesis from Ribosyl Thiourea

A modern and efficient green approach has been developed for the one-pot, solvent-free condensation of β-D-ribosyl thiourea with aryl glyoxals under microwave irradiation on acidic alumina support, affording N-ribonucleosides of 2-thiohydantoin (39a–k) in high yields (Schemes 12 and 13) [23,24]. This method exemplifies sustainable synthesis, being rapid, clean, and waste-minimizing, while the proposed mechanism further supports its applicability as an environmentally friendly alternative.



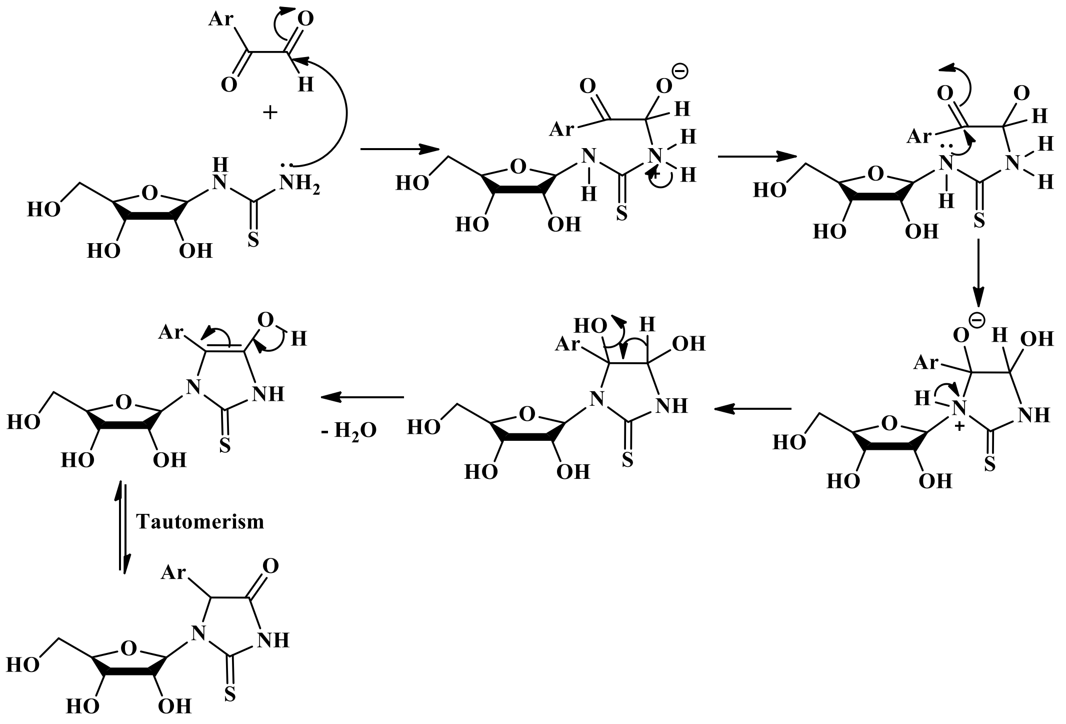
(37) (38,a - K) (39, a - k)

Ar (a-k) = C6H5 , 4-NH2-C6H4 , 2-Cl-C6H4 , 3-Cl-C6H4 , 4-Cl-C6H4 , 2-Br-C6H4,
3-Br-C6H4 , 4-Br-C6H4 , 4-NO2-C6H4 , 3-NO2-C6H4 , 4-CH3O-C6H4

Scheme 12. Microwave-assisted solid-supported synthesis of N-ribonucleosides of 2-thiohydantoin. (39a-k)

2.4.1 Phosphine-Catalyzed and Microwave-Assisted Cyclization

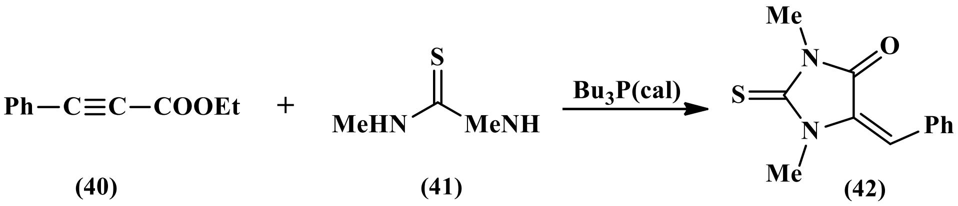
Recent advances in thiohydantoin synthesis highlight both catalytic and microwave-assisted strategies. A sophisticated phosphine-catalyzed approach involves the Bu_3P-catalyzed intramolecular cyclization of arylpropiolates (40) with thioureas (41), following a tandem Umpolung addition–cyclization pathway to afford alkylidene-thiohydantoins (42) in good yields, exemplifying an atom-economical and catalytic methodology [24] . Meanwhile, microwave irradiation has emerged as a powerful tool in organic synthesis, providing rapid and uniform heating that dramatically reduces reaction times while often enhancing yield and purity [25]. This technique has been effectively applied to thiohydantoin synthesis in both one-pot (Scheme 3) and solid-supported methods (Scheme 12). For instance, Smith et al. (2024) [26] reported a microwave-enhanced protocol for the synthesis of 5-arylidene-2-thiohydantoins from amino acids and aryl aldehydes in a deep eutectic solvent, achieving excellent yields in under 10 minutes, demonstrating the potential of combining green solvents with microwave technology.



Scheme 13. Proposed mechanism for synthesis of N-glycosylated 2-thiohydantoins from ribosyl thiourea and aryl glyoxal.

2.4.2. from Cyclocondensation of the derivative thioureas

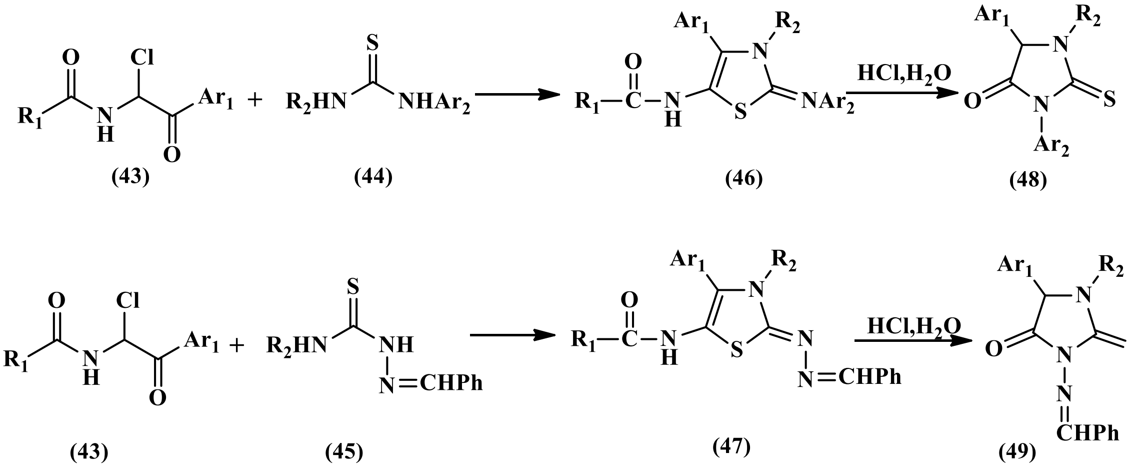
Utilize a phosphine-catalyzed intramolecular cyclization of arylpropiolates and thioureas, as well as a tandem Umpolung addition. As a result, 1,3-dimethyl-5-[(E)-phenylmethylidene]-2-thioxoimidazolidin-4-one (42) is produced in 76% of cases when ethyl 3-phenylpropiolate (40) is intramolecularly cyclized with dimethyl thiourea (41) in toluene under the influence of Bu_3P [25, 26] Scheme 14.



Scheme 14. dimethyl-5-[(E)-phenyl methylidene]-2- thioxoimidazolidin-4-one **(42)**

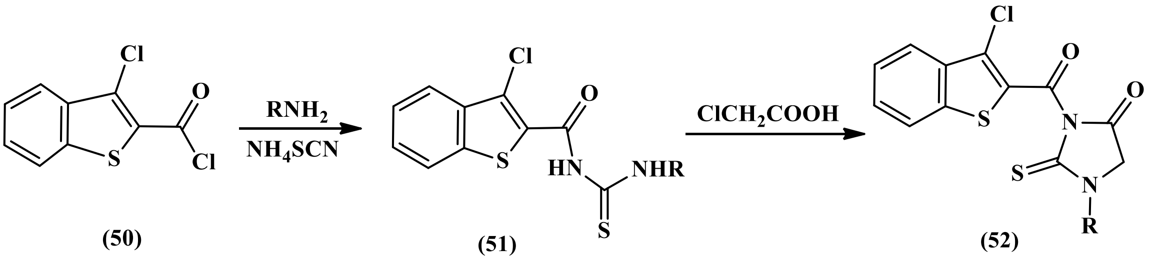
2.4.3 from Cyclocondensation of the derivative thioureas

Thiazole compounds (46) and (47), respectively, were obtained by cyclocondensing N-(2-aryl-1-chloro-2-oxoethyl) carboxamides of the general formula (43) (R_1 = Me, Ph, 4-MeC_6H_4) with thioureas (44) and thiosemicarbazides (45) (R_2 = Me, $CH_2CH_9CH_2$, $PhCH_2$, Ph, 4-$MeOC_6H_4$). Substituted 2-thiohydantoins (48 and 49) were created by recycling and acid hydrolysis of (46) and (47) when heated with hydrochloric acid (Ar_1 = Ph, 4-MeC_6H_4; Ar_2 = Ph, 4-MeC_6H_4, 4-$EtOC_6H_4$) [25, 26] Scheme 15.



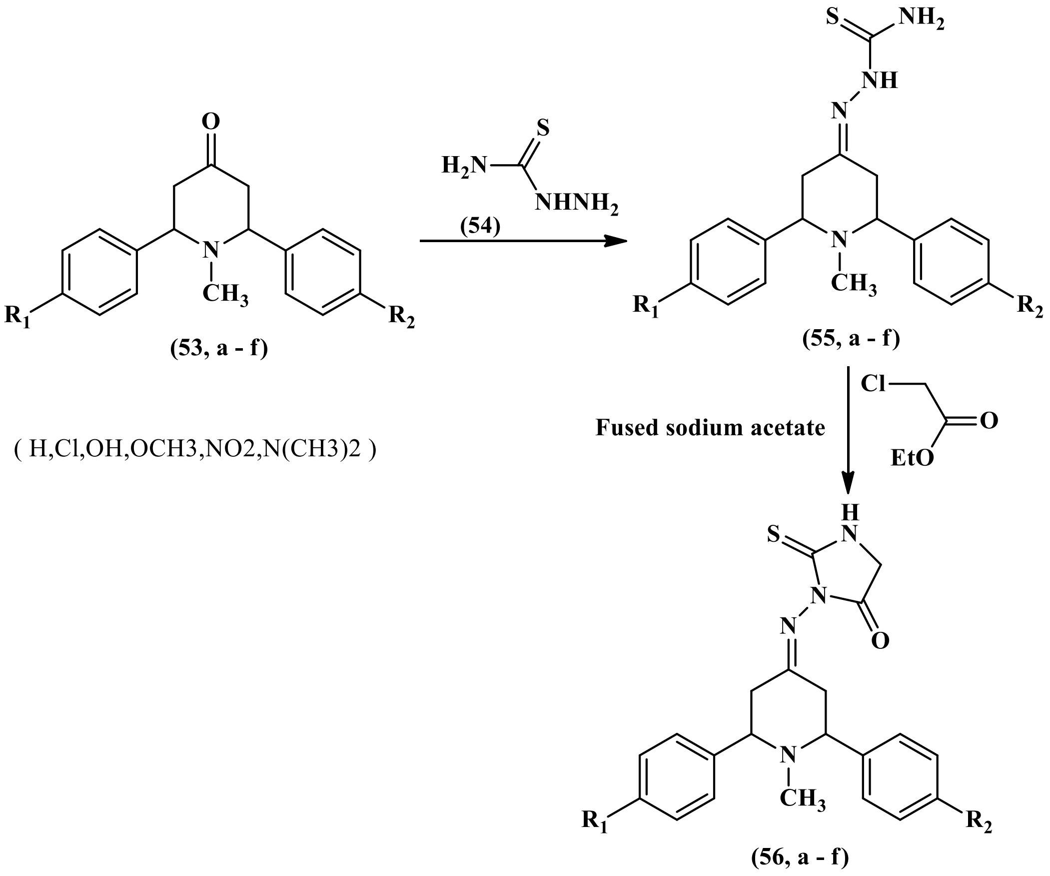
Scheme 15 Synthesis of substituted 2-thiohydantoins **(48-49)**

N-aryl-N' -(3-chloro-2-benzo[b]thenoyl)-thioureas (51) were heterocyclized with chloroacetic acid to provide a sequence of 1-aryl-3-(3-chloro-2-benzo[b]thenoyl)-thiohydantoins (52) [27] Scheme 16.



Scheme 16 Synthesis1-aryl-3-(3-chloro-2-benzo[b]thenoyl)-thiohydantoins **(52)**

Using thio semi carbazide (54) in ethanol, 1-methyl-2,6-diphenylpiperidin-4-thiosemicarbazone (55a-f) is synthesized from 1-methyl-2,6-disubstituted phenyl-piperidin-4-one(53a-f).3-[(1-methyl-2, 6-diphenylpiperidin-4-ylidene)amino] synthesis cyclization of 2-thioxo-imidazolidin-4-one (56a-f) Ethyl chloroacetate, fused sodium acetate, and 1-methyl-2,6-diphenylpiperidin-4-thiosemicarbazone (55a-f) in ethanol [28, 29] Scheme 17.



R1 = R2 (H,Cl,OH,OCH3,NO2,N(CH3)2)

Scheme 17. Synthesis of 3- [(1-methyl-2, 6-diphenylpiperidin-4-ylidene) amino]-2-thioxo-imidazolidin-4-one derivatives(56a-f)

Table 2 shows an overview of advanced and green synthetic methods:

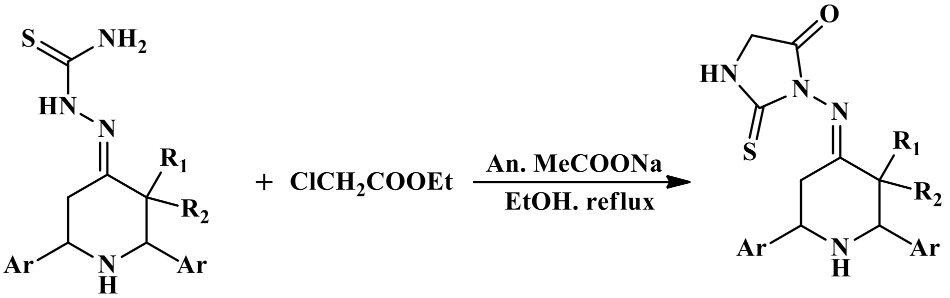
Table 2. Overview of Advanced and Green Synthetic Approaches.

Synthetic Method	Typical Conditions	Green Metrics (E-factor, etc.)	Main Advantages	Ref.
One-Pot Solvent-Free	Neat reaction, heating (Δ)	Excellent (very low E-factor)	Eliminates solvent use, simple workup, high efficiency	[14]
MW-Assisted (Solid Support)	Alumina, microwave irradiation, solvent-free	Excellent	Fast, clean process, high yields, no solvent required	[22]
Aqueous Phase Synthesis	H_2O, P_4O_{10}, room temperature or heating	Very Good	Employs water as a safe and sustainable solvent	[18]
Catalytic Cyclization	Bu_3P (catalytic), toluene, heating	Moderate	Atom economy enables access to structurally complex products	[24]
Deep Eutectic Solvent	DES, microwave, 10 min	Excellent	Biodegradable medium, rapid transformation, high yield	[26]

2.5 Synthesis from Thiosemicarbazone Derivatives

2.5.1.1- derivative thiosemicarbazones

By treating thiosemicarbazones (57) with anhydrous sodium acetate and chloroethyl acetate in refluxing ethanol, heterocycles featuring both piperidine ring systems, such as 3-(3-alkyl-2,6-diarylpiperidin-4-ylidene)-2-thioxoimidazolidin-4-ones (58), could be produced, as shown in Scheme 18.

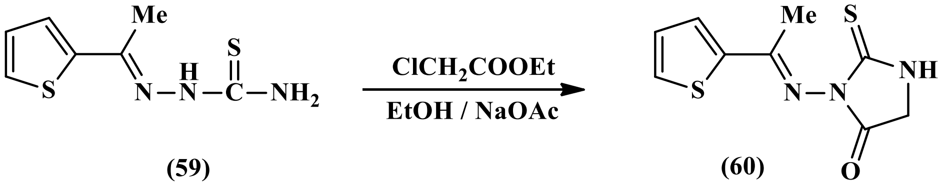


(57) **(58)**

Scheme 18 Synthesis3-(3-alkyl-2,6-diarylpiperin-4-ylidene)-2-thioxoimidazolidin-4-one **(58)**

2.5.**1.2- derivative thiosemicarbazones**

With chloroacetate ethyl 2-acetylthiophene thiosemicarbazone (59) reacts with ethyl chloroacetate to produce thioxoimidazolidinone (60) [30] Scheme 19.

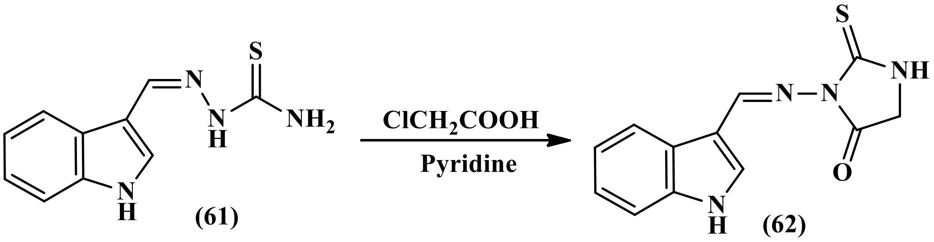


(59) **(60)**

Scheme 19 Synthesis of (E)-3-((1-(thiophen-2-yl) ethylidene) amino)-2-thioxoimidazolidin-4-one (60)

2.5.**1.3- derivative thiosemicarbazones with chloroacetic acid**

indole-3-carbaldehyde thiosemicarbazone **(61)** was condensed with chloroacetic acid in the presence of pyridine to yield 3-[2-Thioxo-imidazolin-4-one-3-yl-imino methylene]-1H-indole **(62)** [31] Scheme 20.

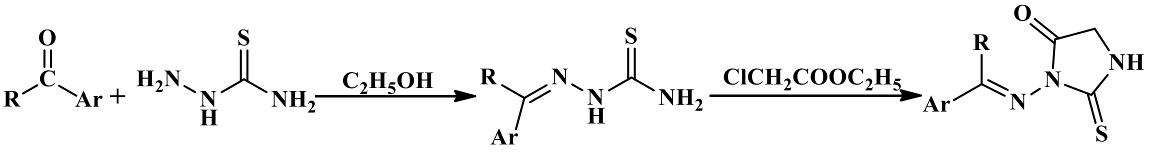


(61) **(62)**

Scheme 20. Synthesis of 3- [2-Thioxo-imidazolin-4-one-3-yl-imino methylene]-1H-indole (62).

2.5.**1.4- Thiosemicarbazone with ketones**

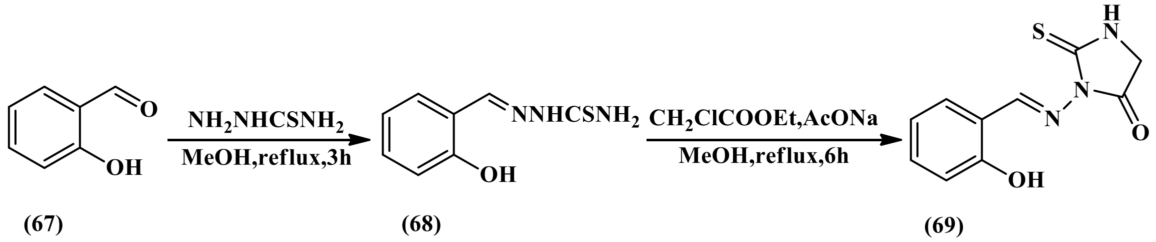
Through the acid-catalyzed condensation of thiosemicarbazide (64) with several ketones (63), including 4-bromoacetophenone, 5-chloroisatin, benzaldehyde, and acetophenone, substituted hydrazine carbothioamide (65) was produced. Ethyl chloroacetate and substituted hydrazine carbothioamides (65) interacted in ethanol under reflux to form the 2-thiohydantoin derivative (66) [32, 33] Scheme 21.



(63) **(64)** **(65)** **(66)**

Scheme 21. Synthesis of 2-thiohydantoin **(66)**.

2.5.1.5- Thiosemicarbazone with aromatic aldahyade [34,35]



Scheme 22. Synthesis of 3-[(2-hydroxybenzylidene) amino]-2-thioxoimidazolidin-4-one.(69)

2.6 Miscellaneous and Advanced Synthetic Routes

To obtain structurally varied 2-thiohydantoin derivatives, several contemporary and alternative methods have been investigated. These include phosphine-catalyzed cyclizations, microwave-assisted processes, and Bucherer-Bergs-type synthesis employing nitriles.

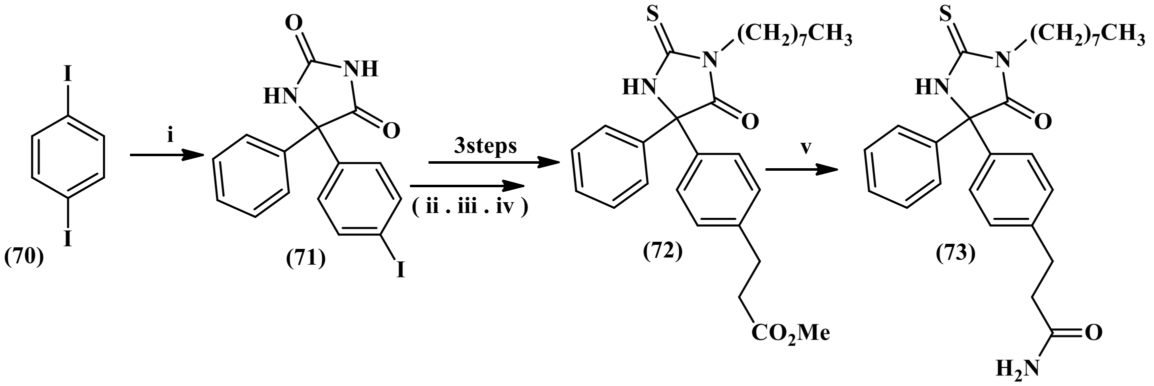
2.6.1- Bucherer-bergs reaction

Montagne *et al.*[36] modified the Butcherer-Bergs reaction, which involved four components (4RC).

Instead of employing ketones as the starting material, nitrile compounds were used to synthesize hydantoin derivatives (Scheme 23).

This process was used to synthesize 2-thiohydantoins. First, the organometallic reagent n-BuLi was treated with 1,4-diiodobenzene (70). Next, nitrile compound (PhCN) and potassium cyanide were added, resulting in 5,5'-disubstituted hydantoin (71).

The subsequent step enabled the selective alkylation reaction at N-3 of this product, followed by a coupling reaction between this product and methyl acrylate in a microwave environment. Lawesson's reagent was effectively utilized to create the thiohydantoin intermediate (72), which was then used to convert hydantoin to thiohydantoin. The intermediate was successful in forming biologically active molecules (73) [37, 38].

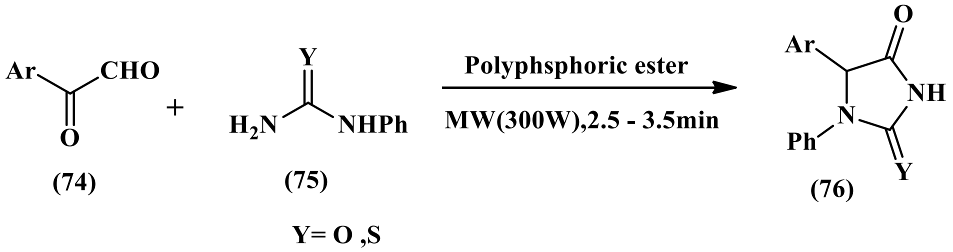


Reagents: i) (1)- n-BuLi, THF, -78 °C. (2)- PhCN, -78 -0 °C. (3)- KCN, $(NH_4)_2CO_3$, 70 °C, EtOH / H_2O (1:1), µW. ii) K_2CO_3, DMF, $Me(CH_2)_7Br$. iii) $MeO_2CCH{=}CH_2$, $Pd(OAc)_2$, Bu_3N, DMF, 100 °C, µW. iv) (1)- H_2, Pd/C, MeOH, r.t. (2)- Lawesson's reagent, PhMe, 110 °C. v) (1)- LiOH, THF/H_2O (1:1). (2)- NH_3, HOBt, PyBO, DMF, r.t.

Scheme 23. Synthesis of 2-thiohydantoins derivatives from phenyl iodide

2.6.2-from microwave-assisted synthesis

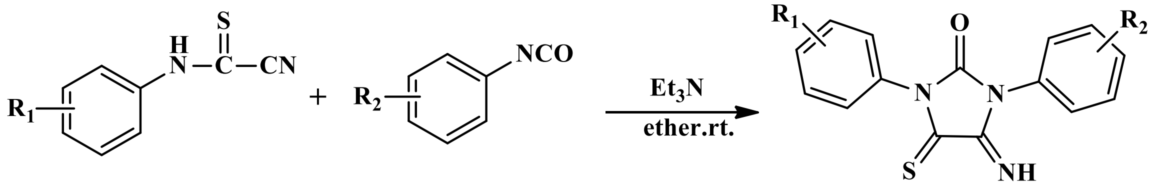
Microwave-assisted synthesis of hydantoins and thiohydantoins (76) from an \alpha-ketoaldehyde (74) and a substituted urea or thiourea (75) using polyphosphoric ester (Scheme 24).



Scheme 24. Some syntheses of hydantoins and thiohydantoins.

2.6.3- from aromatic cyanothioformanilides and derivative isocyanates

With triethylamine as a base, phenyl-, p-chlorophenyl-, p-chloro-3-trifluromethyl-, and 2,4,5-trichlorophenyl isocyanates in ether were used in the heterocyclic ring-closing reactions of different aromatic cyanothioformanilides (77) (R_1 = p-Me, p-OMe, p-OEt, p-Cl, p-Br, p-I, 3,4-Cl) to produce the corresponding 5-imino-4-thioxo-2-imidazolidinones, with 65–70% yields (79), scheme 25.



(77) **(78)** **(79)**

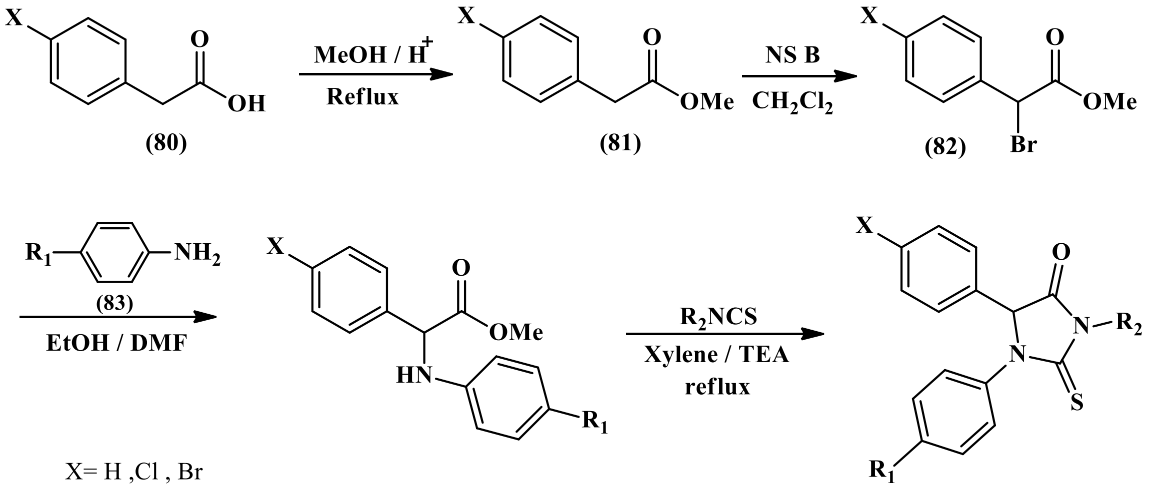
Scheme 25. Synthesis of 2-thiohydantoins derivatives (79)

2.6.4-From carbonyl compounds

1,5-Diaryl-2-thiohydantoins (85) were produced from phenylacetic acids by esterification, bromination, C-N bond formation, and cyclization (as cyclooxygenase-2 inhibitors).

N-bromosuccinimide was used to bromate (81) in dichloromethane at room temperature. The amines (84) were produced by reacting bromides (82) with sulfanilamide, p-anisidine, and aniline in ethanol (or *N,N*-dimethyl-formamide).

Triethylamine and potassium thiocyanate were used to treat amines (84) to create thiohydantoins (85) from them, scheme 26.



X= H ,Cl , Br

R1 = H , OMe , SO2NH2

R2 = butyl , pentyl , phenyl , benzyl

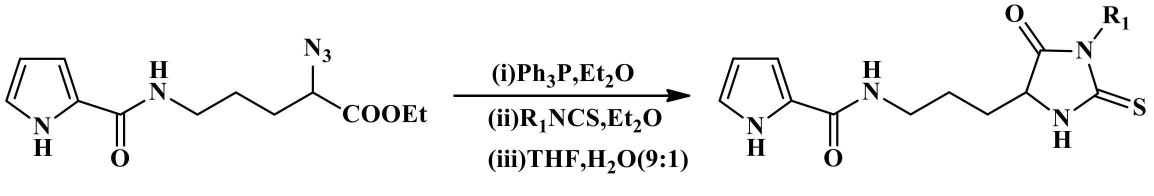
(84) **(85)**

Scheme 26 Synthesis of 2-thiohydantoins derivatives (85)

2.6.5- α-Azido ester

2.6.5.1- α-Azido ester with isothiocyanate

The α-azido ester (86) was successively treated with triphenylphosphine and isothiocyanates to produce the thiohydantoins (87) in yields of 60–75%. Scheme27.

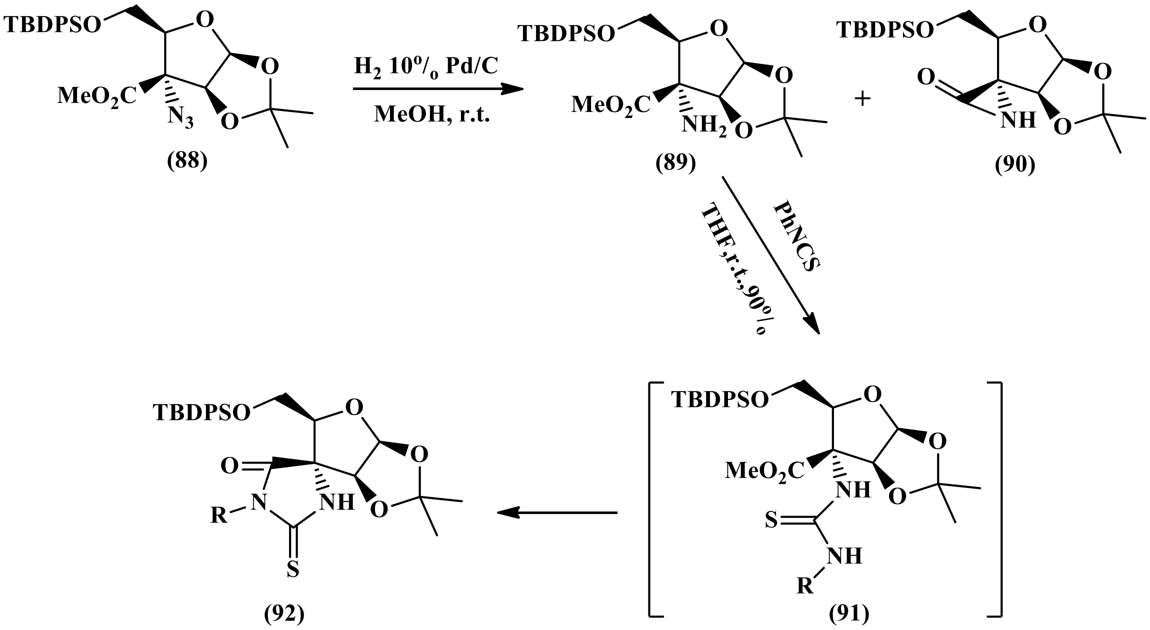


(86) R1 = Me,Et,Pr,Bn **(87)**

Scheme 27 Synthesis of compound (87)

2.6.5.2 - Catalytic hydrogenation of α-azidoester

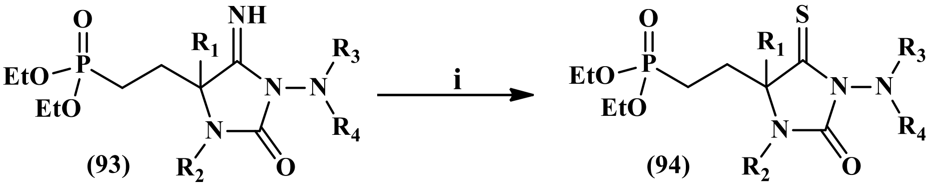
Synthesis of a bicyclic thiohydantoin derivative (92) via catalytic hydrogenation of an \alpha-azidoester (88) to form an amine (89), followed by reaction with phenyl isothiocyanate (PhNCS) (Scheme 28).



Scheme 28. Catalytic hydrogenation of α-azidoester **(88)**.

2.6.6 - 4-Imino-imidazolidin-2-one derivatives

3-amino-4-imidazolidin-2-one derivatives (93) were thionated by hydrogen sulfide in dry dichloromethane with dry pyridine present, which produced 3-amino-4-thioxo-imidazolidin-2-one (94) Scheme 29.

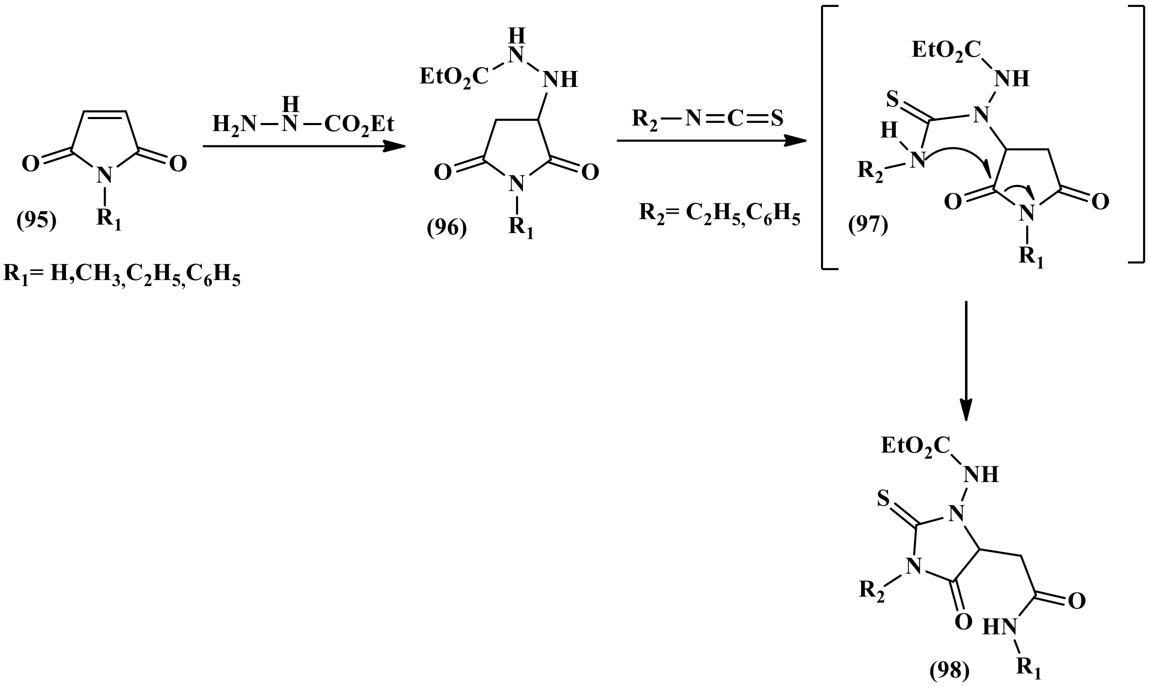


R1 = CH3 , R2=R3=H , R4=C6H5,4-C6H4,H,t-Bu

Scheme 29. Synthesis of 3-amino-4-thioxo-imidazolidin-2-one **(94)**

2.6.7- N-substituted maleimide

The production of 3,4-dihydromaleimides (96) from Michael's addition of 3-ethylhydrazinoacetate to N-substituted maleimide (95) resulted in a smooth reaction with substituted isothiocyanates to produce compounds (98) (Scheme 30).



Scheme 30. Synthesis of 2-thioxoimidazolidin-4-one derivatives **(98)**.

3. Conclusion

This review has provided a thorough examination of the diverse synthetic strategies for constructing the 2-thiohydantoin scaffold, encompassing both classical foundational approaches and contemporary cutting-edge methodologies. The evolution of these synthetic routes clearly reflects a trend towards greener, more efficient, and sustainable processes. Key advancements are summarized as follows:

1. **Integration of Green Chemistry Principles:** The implementation of solvent-free reactions, one-pot multicomponent protocols, aqueous reaction media, and microwave-assisted synthesis significantly reduces environmental impact while enhancing reaction efficiency.

2. **Catalytic Strategies:** The development of catalytic systems, such as phosphine-catalyzed cyclizations, enhances atom economy and facilitates access to structurally complex and diverse thiohydantoin derivatives.

3. **Process Intensification:** Techniques such as microwave-assisted and flow chemistry enable rapid and uniform synthesis, making them particularly suitable for high-throughput screening and drug discovery applications.

Despite these advancements, several challenges and promising avenues for future research remain:

- **Enantioselective Synthesis:** Many existing methods generate racemic mixtures. Developing asymmetric catalytic routes to enantiopure thiohydantoins remains a critical objective for medicinal chemistry and pharmaceutical applications.

- **Scalability:** While many modern methods are efficient on a laboratory scale, their applicability to industrial-scale production requires further validation.

- **C–H Functionalization:** The incorporation of direct C–H activation strategies could provide more streamlined and atom-economical pathways to diversify the thiohydantoin core.

- **AI and Machine Learning Integration:** Computational tools and machine learning offer significant potential for predicting reaction outcomes, optimizing reaction conditions, and designing novel thiohydantoin derivatives with desired chemical and biological properties.

In conclusion, the synthetic toolkit for 2-thiohydantoins is both extensive and versatile. By carefully selecting and adapting the appropriate methodologies, researchers can efficiently generate novel derivatives for applications in pharmaceutical development, materials science, and other domains. This review serves as a practical guide for selecting synthetic strategies that strike a balance between efficiency, sustainability, and the specific requirements of the target compounds.

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