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Thiadiazole and Its Derivatives: Emerging Synthetic Methods Using Thiosemicarbazides and Hydrazides

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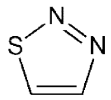
Abstract: *Thiadiazoles and their derivatives have attracted considerable interest due to their wide-ranging pharmacological and industrial applications. Recent progress in their synthesis has predominantly centered on the use of thiosemicarbazides and hydrazides as fundamental precursors. Various catalytic and non-catalytic methodologies, including green chemistry approaches, microwave-assisted techniques, and solvent-free conditions, have been explored to improve efficiency and yield. Structural modifications of thiadiazoles have resulted in compounds exhibiting enhanced biological activities, such as antimicrobial, anticancer, and anti-inflammatory effects. This review provides an overview of recent advancements in synthetic strategies, reaction mechanisms, and novel applications of thiadiazole derivatives, with a focus on sustainable and cost-effective methods*

Keywords: Thiadiazole, thiosemicarbazides, hydrazides, green chemistry, catalytic methods, biological activities

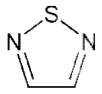
I. INTRODUCTION

Heterocyclic compounds are important to medicinal chemists because of their exceptional chemical properties and wide range of biological activities. Thiadiazole is a common and important fivemember heterocyclic system containing two nitrogen atoms and a sulphur atom [1].The ring is aromatic and it has four constitutional isomers differing by the relative positions of the sulfur and nitrogen atoms. Thefour isomers of thiadiazoles are 1,2,3- thiadiazoles, 1,2,4-thiadiazoles, 1,2,5-thiadiazoles and 1,3,4-thiadiazoles.



1,2,3- thiadiazole

1,2,4-thiadiazole



1,2,5-thiadiazole

1,3,4-thiadiazole

Fig.1 Isomers of thiadiazole

Among the four isomers, 1,3,4-thiadiazoles are the most importantisomer having antitumoral potential [2]. These compounds have very important applications in the field of agrochemicals, pharmaceuticals, and material research. They demonstrate diverse biological effects, including antifungal [3], antibacterial [4], anti-inflammatory [5], antiparasitic [6], antioxidant [7], antidepressant [8], anticonvulsant [9], diuretic, and antitumoral activities [10].These biological activities encouraged researchers to find out different methods for synthesis of new and existing thiadiazoles and their derivatives using different starting materials thiosemicarbazides,thiocarbazides, dithiocarbazates, thioacylhydrazines, acylhydrazines, and bithioureas [11–17].This review is useful for researchers for the preparation of thiadiazole derivatives, drug discovery, and medicinal chemistry.

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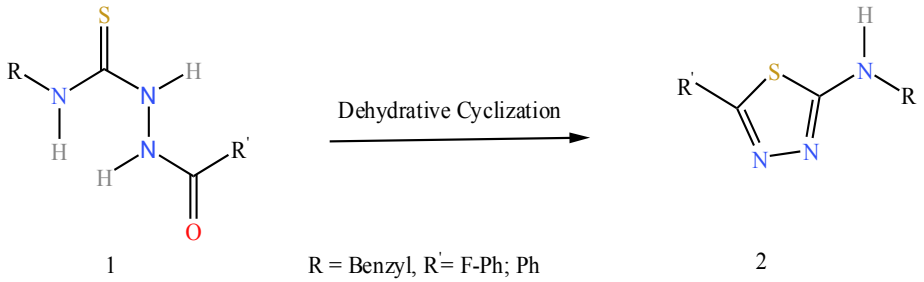
Methodologies for the synthesis of thiadiazole and its derivatives

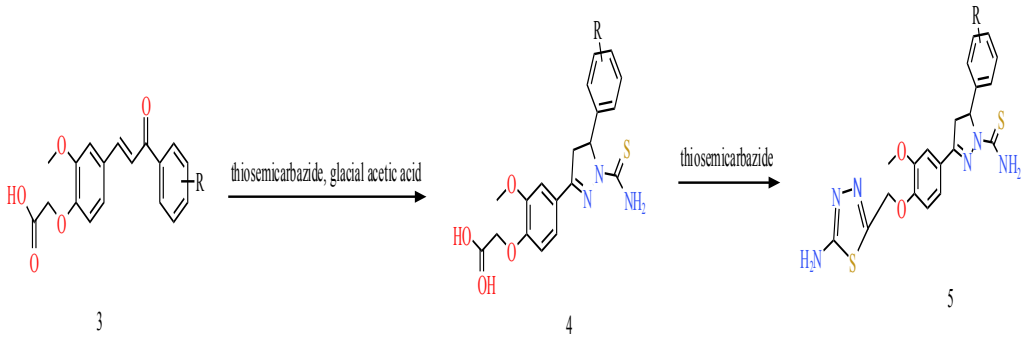
From thiosemicarbazides

In 2013, Yang and co-authors have prepared 2-amino-substituted thiadiazole derivatives (2). This method involves the preparation of intermediate thiosemicarbazides (1)[18].



Scheme 1. Schematic diagram of thiosemicarbazide cyclization

In 2011, Malleshappa N. Noolvi and co-authors synthesized novel 1,3,4-thiadiazole derivatives (5) of 2-(4-formyl-2-methoxyphenoxy) acetic acid by cyclization of carboxylic acid group with thiosemicarbazide (3) in the presence of POCl3 or PPA [19].



Scheme 2. thiadiazole derivative compound from thiosemicarbazide.

In 2018 Mehlika Dilek Altıntop and co-authors were synthesized 1,3,4-thiadiazole derivatives(8) using (4-(trifluoromethyl)phenyl) thiosemicarbazide(6) and carbon disulfide, the intermediate formed further treated with N-(aryl)−2-chloroacetamides (24), in the presence of catalyst K2CO3 in acetone and they studied for their cytotoxic effects on multiple human cancer cell lines[20]. (Scheme 3)

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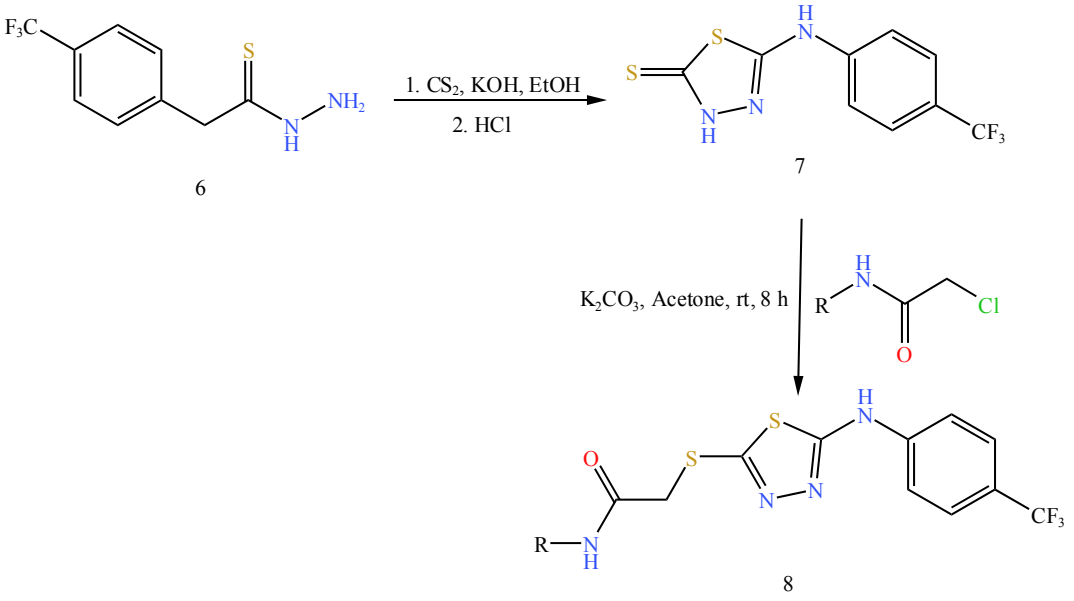
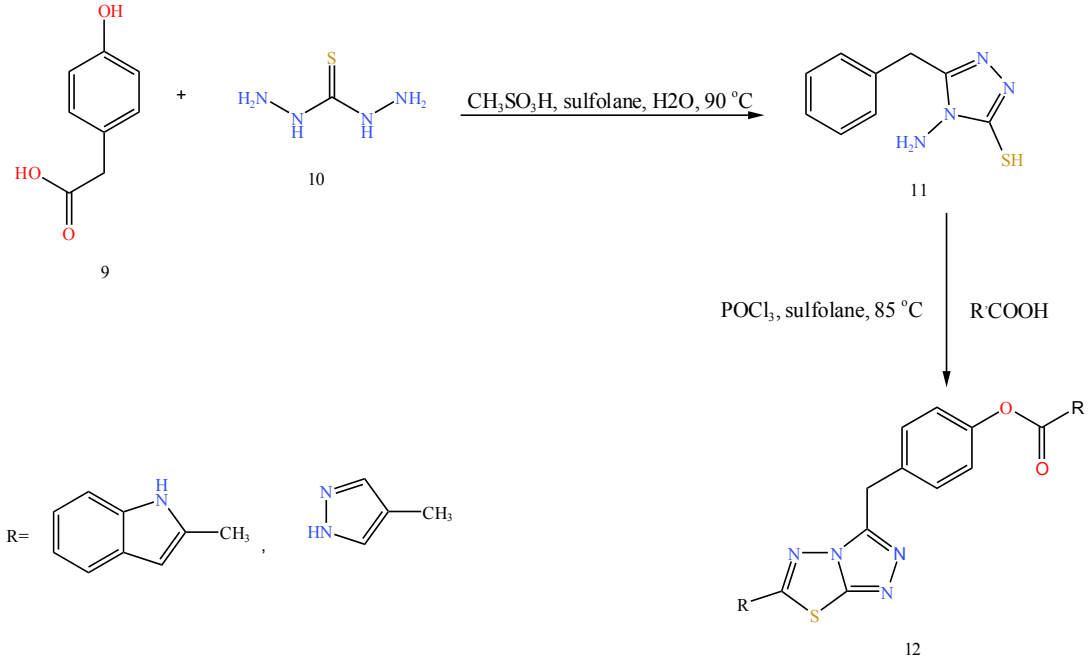


Scheme 3. 1,3,4-thiadiazole synthesis using thiosemicarbazide and CS2

In 2018 Yuan and colleagues synthesized triazole-based thiadiazole derivative (12) in two step.First they have prepared intermediate (11) by dissolving aromatic carboxylic acid(9) and thiosemicarbazide(10) in a solvent which is mixture of sulfolane and water. The intermediate was further treated with aromatic carboxylic acid and $POCl_3$ catalyst in sulfolane at 85°C for 18 h. [21].(Scheme 4)



Scheme 4. Synthesis of triazole-based thiadiazole derivatives

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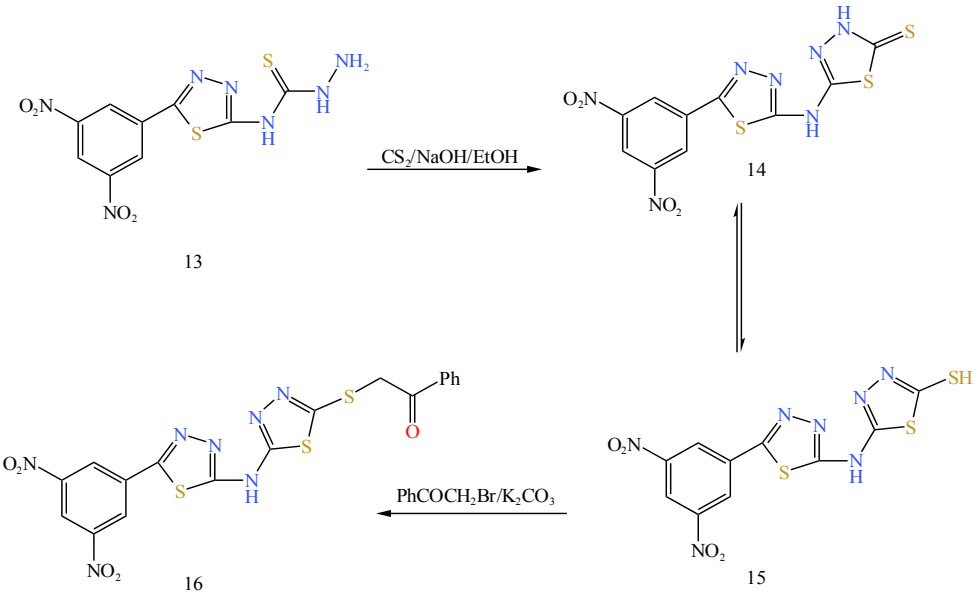
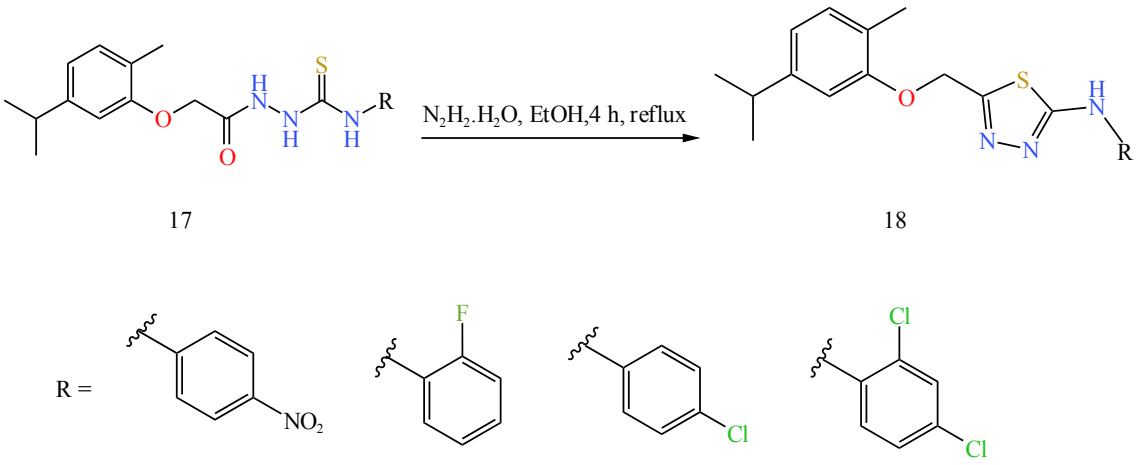
In 2019 Mohamed El-Naggar and coauthors prepared 1,3,4-thiadiazol-2-yl derivatives (14 & 15) by treating thiosemicarbazide derivatives (13) with CS_2 / NaOH in ethanol. 1,3,4-thiadiazol-2-yl derivative (13) after treating with phenacyl bromide in the presence of potassium carbonate gives acetophenone derivatives (16)[22]. (Scheme 5)



Scheme. 5 Synthesis of bis-thiadiazoles

In August 2023 Tenzile Alagöz and coauthors were obtained thiosemicarbazide derivatives (17) fromethylphenoxy acetate derivative and hydrazine hydrate. Then the intramolecular cyclisation of thiosemicarbazide derivative (17) carried out in acidic medium to synthesize triazole-3-thiol derivatives (18)[23]. (Scheme 6)



Scheme. 6 thiosemicarbazide and 1,3,4 thiadiazole derivatives

In 2022 Hakan S. Sayiner and coauthors synthesized1,3,4-Thiadiazole derivative (21) usingmethoxy cinnamic acid (19)and phenylthiosemicarbazide (20) in the presence of phosphorus oxychloride [24]. (Scheme 7)

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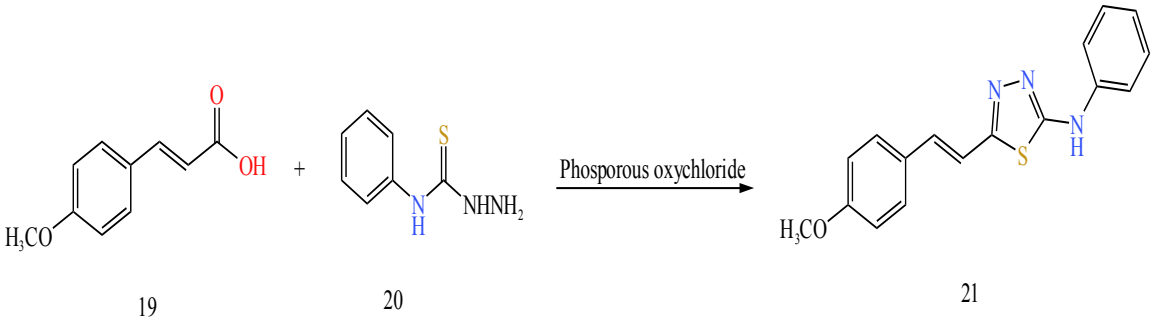
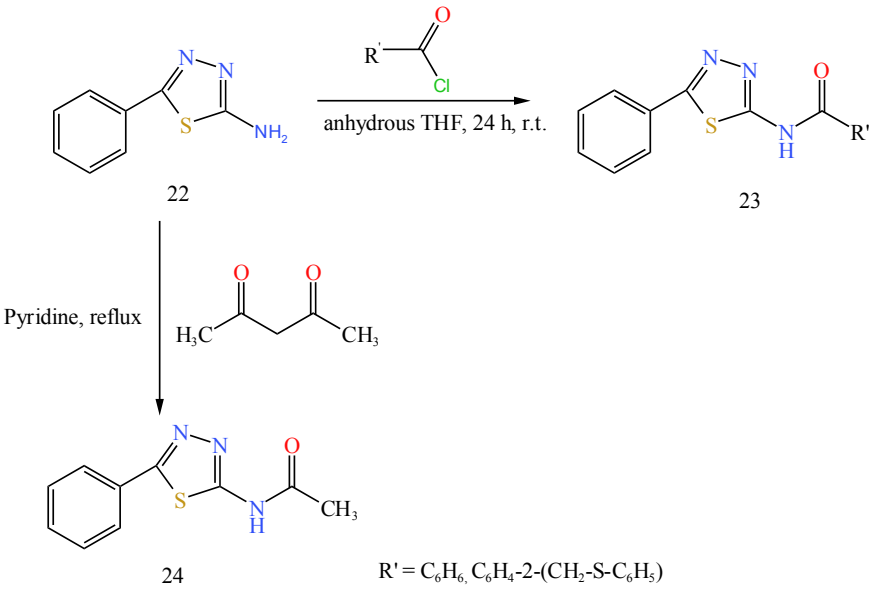


19 20 21

Sceheme 7. Synthesis of thiadiazole derivative using thosemicarbazide derivative

Camelia ElenaStecoza and colleagues prepared 1,3,4-Thiadiazole-2-amide derivatives (23) by coupling reaction between 5-phenyl-1,3,4-thiadiazol-2-amine and corresponding acid chlorides in anhydrous tetrahydrofuran (THF) and 1,3,4-Thiadiazole-2-amide derivatives (24) obtained by acetylation of (22). Liberated hydrogen chloride is neutralized by using solid sodium hydrogen carbonate[25]. (Scheme 8).



22 23 24

Scheme 8. Synthesis of 1,3,4-thiadiazol-2-amide derivatives.

From Hydrazides

In 2013Dinneswara Reddy Gudawere synthesized *2*-amino-1,3,4-thiadiazoles hydrazine by refluxingtrimethylsilyl isothiocyanate in ethanol then acidified it with conc. H_2SO_4 [26].

In 2017Maaroof Zarei were carried out synthesis of 1,3,4-thiadiazoles. In this method carboxylic acids (25) and hydrazine (26) were converted to 1,3,4-thiadiazoles (28)in the presence of Vilsmeier and Lawson's reagent [27]. (Scheme 9)

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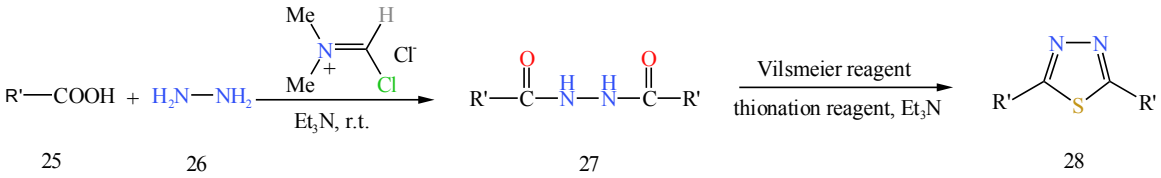
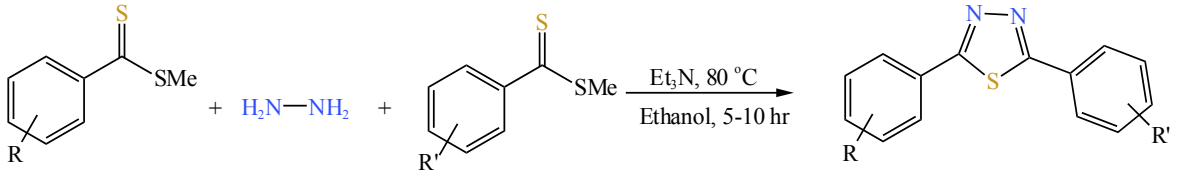


25 26 27 28

Scheme 9. Synthesis of 1,3,4-thiadiazoles

In 2019Kemparajegowda and coauthors were synthesized 3,5-disubstituted 1,3,4-thiadiazole(31)from dithioesters (29& 30), hydrazine hydrate and triethyl amine[28].(Scheme 10)

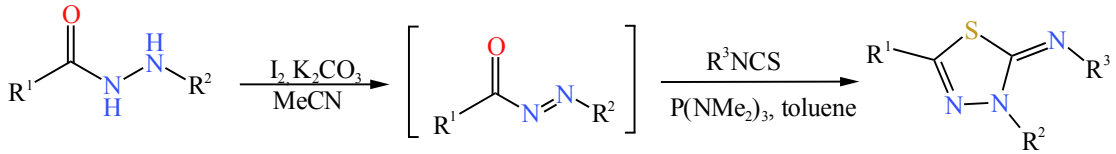


29 30 31

R and R' = Me, OMe, F, Cl, OH

Scheme 10. Synthesis of 3,5-disubstituted 1,3,4-thiadiazole using hydrazine

In 2020 Zhengyan Huang and colleagues synthesized 2-Imino-1,3,4-thiadiazoles(33) from Hydrazides (32) and Isothiocyanates via Sequential Oxidation and $P(NMe_2)_3$-Mediated Annulation reactions [29].(Scheme 11)

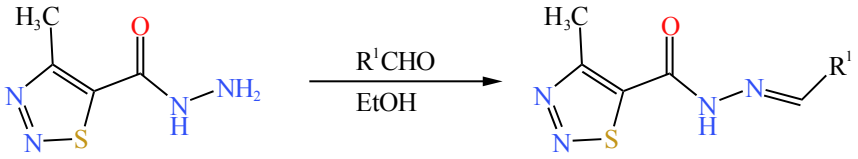


32 33

R^1 and R^2 = Ph, CN, Me, Cl , NO_2

Scheme 11. 2 Imino-1,3,4-thiadiazoles

In 2021 Kinga Paruch and co-authors synthesized derivatives of 4-methyl-1,2,3-thiadiazole-5-carboxylic acid hydrazide (35). Hydrazide (34) and aldehyde in ethanol is refluxed for 3 hours then it placed in a refrigerator for 24 hrs. The formed derivative was filtered off and recrystallized from ethanol [30].(Scheme 12)



34 35

R^1= 2-Cl-C_6H_4, 3-Cl-C_6H_4, 2-F-C_6H_4, 4-F-C_6H_4, 3-OC_2H_5-4-OH-C_6H_3

Scheme 12. Synthesis of derivatives of 4 methyl 1,2,3 thiadiazole 5 carboxylic acid hydrazide

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II. CONCLUSION

This review paper gives information about recent progress in the synthesis of thiadiazole and its derivatives using thiosemicarbazides and hydrazides in both methodology and applications. These compounds, characterized by their versatile biological and pharmacological properties, have become valuable targets in medicinal chemistry. The use of thiosemicarbazides and hydrazides as key intermediates in thiadiazole synthesis has proven to be an effective approach, offering improved yields, selectivity, and reaction conditions. Additionally, innovative strategies such as green chemistry principles and catalytic processes have been integrated into synthetic routes, enhancing the sustainability and efficiency of these reactions. The structural diversity and reactivity of the resulting thiadiazole derivatives, particularly in the context of their potential applications in drug development, make them promising candidates for future research. As the understanding of their chemical properties continues to expand, these compounds hold the potential to contribute significantly to the development of new therapeutics, making them a highly relevant subject of ongoing investigation.

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