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Streamlined Green Synthesis and Process Optimization for Tetrazole Derivatives Via Metal-Free Reactions

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KEYWORDS

Active pharmaceutical ingredients (APIs), Sartan drugs, Green synthesis, [3+2] cycloaddition, (CSPH) Catalytic systems

ABSTRACT:

Introduction: This work presents a pioneering approach to in situ tetrazole formation for active ingredients, achieving high yields and eco-friendly outcomes. This innovation is significant for sartan drugs, essential in hypertension treatment. The study addresses synthetic challenges, functionalization, and applications of poly-nitrogen heterocyclic compounds, revealing novel conditions for tetrazole synthesis utilizing versatile catalytic systems and advanced techniques. With a focus on green synthesis, the research steers towards impactful areas in tetrazole chemistry. The [3+2] cycloaddition of sodium azide to nitriles, efficiently catalyzed by a Copper (II) complex, yields 5-substituted 1H-tetrazoles. This method reduces risks associated with spark discharge and nitrogen gas explosions, with structural characterization confirming its effectiveness. Consistent results across various derivatives underscore the method's potential for developing new active pharmaceutical ingredients (APIs). The active compound was characterized using IR, PMR, CMR, and mass spectrometry, highlighting the necessity for continuous innovation in this field.

Objectives: The objective of this research is to develop an innovative, eco-friendly method for in situ tetrazole formation, enhancing the synthesis of sartan drug APIs through optimized [3+2] cycloaddition of sodium azide to nitriles catalysed by a Copper (II) complex, with a focus on high yield, safety, and novel pharmaceutical applications.

Methods: In this research, focused on developing a sustainable method for synthesizing tetrazoles, key compounds in drug development. Using a [3+2] cycloaddition reaction between sodium azide and nitriles, we employed a Copper (II) catalyst to achieve high yields under safer, greener conditions. This approach not only minimizes environmental risks like spark discharge and nitrogen gas explosions but also enhances the efficiency of the process. We used advanced techniques such as IR, PMR, CMR, and Mass Spectrometry to carefully analyse and confirm the structure and quality of the tetrazoles produced, ensuring their suitability for pharmaceutical applications.

Results: This study presents an efficient, eco-friendly method for synthesizing 5-substituted 1H-tetrazoles using copper sulfate pentahydrate as a catalyst in a one-pot process with DMSO. The method improves yields, avoids toxic reagents, and streamlines API production, offering a versatile, scalable solution for pharmaceutical synthesis.

Conclusions: In conclusion, this study presents a novel and efficient synthesis route for 1H-tetrazoles, utilizing a copper (II) complex with a tetradentate ligand under mild conditions. Employing green solvents and non-toxic reagents, the method adheres to sustainable chemistry principles, offering improved efficiency and scalability for API development. These findings underscore the potential of innovative, eco-conscious synthetic pathways in advancing pharmaceutical manufacturing.

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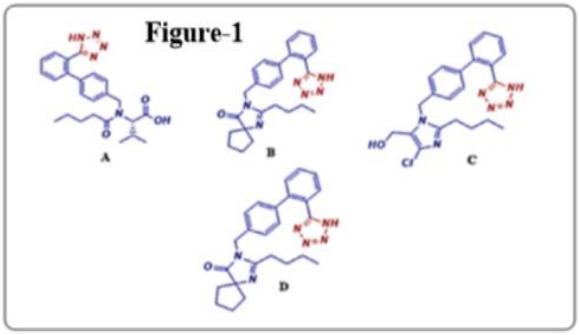
1. Introduction

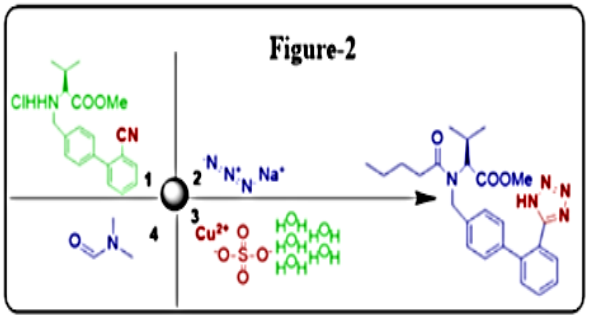
Triazoles, five-membered heterocyclic compounds with three nitrogen atoms, exhibit significant biological activities and are widely used in pharmaceuticals, agrochemicals, and materials science. Traditionally synthesized via metal-catalyzed methods like Huisgen 1,3-dipolar cycloaddition, these processes face challenges such as toxicity, environmental hazards, high costs, and substrate sensitivity. Tetrazole formation, essential for sartan APIs in antihypertensive agents, enhances drug activity and pharmacokinetics by increasing binding affinity to angiotensin II receptors and improving metabolic stability**.** Recent green chemistry advancements have made tetrazole synthesis more efficient and eco-friendly, particularly through the [3+2] cycloaddition of sodium azide to nitriles, catalyzed by Copper (II) complexes. **[1]** This method not only yields high-quality tetrazoles but also mitigates the risk of spark discharge and potential explosions due to nitrogen gas generation, a common hazard in traditional synthesis methods.The efficiency and safety of this catalytic process are validated by consistent results across various tetrazole derivatives. Structural characterization of the resulting tetrazoles confirms the reliability of this method, making it valuable for synthesizing new APIs. **[2-3]** the success of this synthesis route underscores the importance of ongoing innovation in tetrazole chemistry, opening new avenues for developing more effective and sustainable sartan drugs. Furthermore, the focus on green synthesis aligns with broader goals of reducing the environmental impact of pharmaceutical manufacturing. Eco-friendly processes not only improve the sustainability of drug production but also ensure scalability for industrial applications. This commitment to green chemistry addresses the environmental challenges posed by traditional methods, paving the way for a more sustainable pharmaceutical industry **[4-7].** Tetrazole formation is crucial for synthesizing sartan APIs, enhancing their therapeutic efficacy and metabolic stability. Advances in green chemistry and innovative catalytic systems have significantly improved tetrazole synthesis's efficiency and safety, promising more sustainable drug development. Tetrazoles, unique for their high nitrogen content, enhance drug activity by increasing biodisponibility and serve as bioisosteric replacements for carboxylic acids. They are valuable in medicinal chemistry, pharmaceuticals, explosives, high-energy materials, coordination complexes, and as organ catalysts.



Valsartan, Irbesartan, and Losartan, angiotensin II receptor blockers, effectively treat hypertension and heart failure due to the (1H-tetrazol-5-yl) biphenyl fragment enhancing target protein binding. **[8-14]** Research on modified benzo furan and tetrazole derivatives aims to improve hypertension treatments, enhancing global availability and affordability, and underscoring their importance in cardiovascular disease management.

SELECTION OF GREEN SOLVENT

Selecting a green solvent involves evaluating sustainability, safety, and environmental impact, with options like water, supercritical CO_2, ionic liquids, bio-based solvents, and biodegradable solvents such as dimethyl carbonate, ethyl lactate, and propylene carbonate, depending on application, compound characteristics, cost, and regulatory compliance.



Dimethyl sulfoxide (DMSO) is a green, non-toxic, biodegradable solvent effective for many compounds but unable to dissolve PVC, highlighting the need for green solvents that can handle specific materials. Despite this limitation, DMSO remains valuable in various industries, with ongoing research focused on developing new

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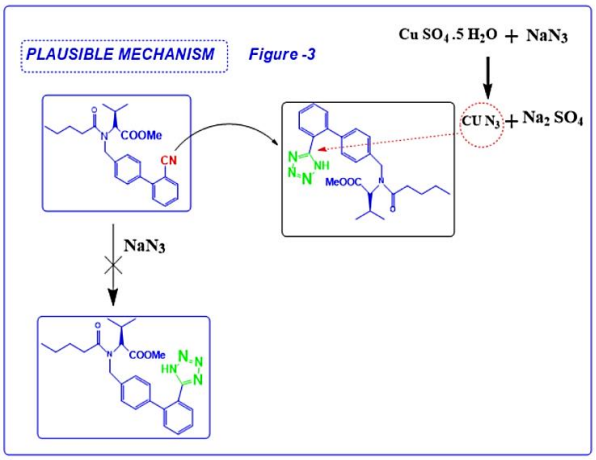
solvents for a broader range of materials. **[15-19].** Tributyltin chloride, a potent Lewis acid catalyst, facilitates various organic reactions using tin, whereas copper sulfate pentahydrate ($CuSO_4•5H_2O$) serves as a sustainable, metal-free catalyst, crucial for forming tetrazoles from nitriles and sodium azide by providing Cu^{2+} ions that enhance reactivity and align with green chemistry principles. **[20-22].** Regeneration of Catalyst After tetrazole ring formation, Cu^{2+} ions are released for reuse in catalytic cycles, with literature showing the catalyst can be recycled up to three times without significant yield loss. Additionally, residual Cu_2O waste can be converted back into $CuSO_4•5H_2O$ using H_2O_2 and H_2SO_4, achieving 97% copper recovery.



Copper sulfate pentahydrate ($CuSO_4•5H_2O$) acts as a sustainable catalyst in tetrazole formation via cycloaddition, releasing Cu^{2+} ions that enhance azide reactivity with nitriles and can be recycled, offering an efficient, mild, and green alternative to traditional metal catalysts for pharmaceutical synthesis.

2. Objectives

Our objective is to pioneer a sustainable and efficient synthesis method for tetrazole derivatives, thereby enhancing the safety, scalability, and environmental responsibility of pharmaceutical manufacturing.

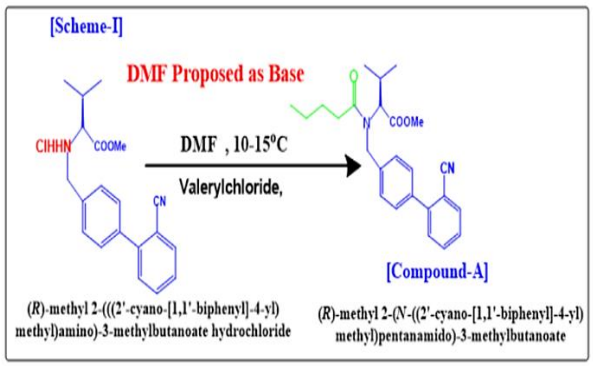
The primary objective of this research is to develop a sustainable and highly efficient synthesis method for tetrazole derivatives. By employing green chemistry principles and leveraging innovative catalytic systems, this approach aims to improve both the safety and scalability of pharmaceutical manufacturing. The synthesis process focuses on minimizing the use of hazardous reagents, while ensuring high yields and selectivity in the formation of tetrazoles, which are critical components in active pharmaceutical ingredients (APIs).

In addition to enhancing safety and efficiency, this method also emphasizes environmental responsibility by reducing the generation of toxic by-products and utilizing eco-friendly solvents. The scalable nature of the process allows for broader industrial application, promoting more sustainable pharmaceutical manufacturing practices. Through this research, we aim to contribute to the development of greener and more responsible methods for producing essential medicinal compounds.

EXPERIMENTAL SECTION

All chemicals were sourced from commercial suppliers and used without further purification. Reagents were purified by distillation, and deuterated solvents for spectroscopy were from Sigma-Aldrich. TLC was performed on Merck 1.05554 silica gel sheets, with spot visualization under UV light or iodine. Column chromatography used silica gel (60−120 mesh). NMR spectra were recorded on a Bruker Advance III 400 MHz spectrometer, with chemical shifts reported in ppm. ESI mass data were collected using a WATERS−XEVO G2-XS-QToF mass spectrometer, and IR and UV−vis spectra were recorded on Thermo-Scientific Nicolet iS50 and Agilent Cary 60 spectrophotometers, respectively.

Scheme-I ((R)-methyl 2-(N-((2'-cyano-[1, 1'-biphenyl]-4-yl) methyl) pentanamido)- 3-methylbutanoate



In the reaction depicted in **Scheme-I,** dimethyl formamide (DMF) serves a dual role as both a solvent and a mild organic base. This innovative approach replaces traditional inorganic bases such as sodium

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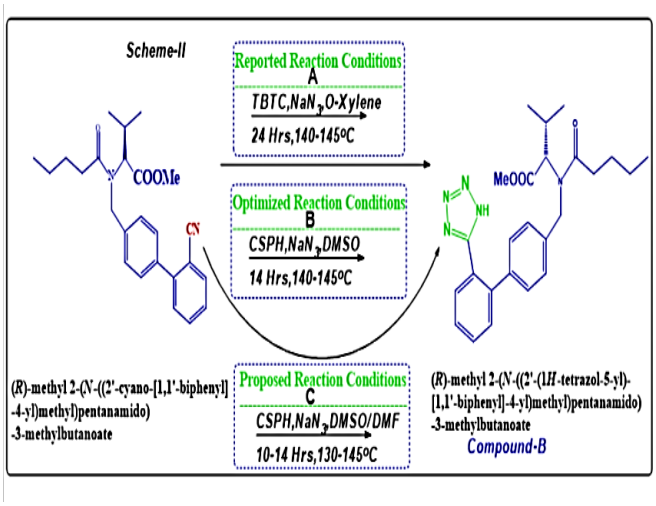
carbonate, which are typically used in similar reactions. By functioning as a solvent, DMF enhances the solubility of both the reactants and the products, ensuring a more efficient condensation process.

Furthermore, as a mild organic base, DMF promotes the bond formation between valeryl chloride and the other reactants, facilitating a smoother and more controlled reaction. This dual functionality not only simplifies the reaction setup but also improves the overall efficiency and yield of the process, showcasing DMF's effectiveness in optimizing reaction conditions.

Scheme-II: (R)-Methyl 2-(N-((2'-(1H-tetrazol-5-yl)-[1, 1'-biphenyl]-4-yl) methyl) pentanamido)-3-methylbutanoat



The above scheme indicate that copper sulfate pentahydrate (CSPH) serves as a superior catalyst compared to copper chloride (CC) and copper acetate (CAC) in the synthesis of tetrazole derivatives. Specifically, when CSPH is used as a catalyst in water or dimethyl sulfoxide (DMSO), it consistently yields higher results. Notably, the highest yield of 95% is achieved when CSPH is employed in DMSO. This optimal performance in DMSO suggests that the solvent significantly enhances the catalytic efficiency of CSPH, likely due to its ability to facilitate better solvation and stabilization of intermediates during the reaction. The improved yield demonstrates CSPH's effectiveness in promoting the [3+2] cycloaddition reaction, underscoring its advantage over other copper-based catalysts. The use of DMSO, a green solvent, further supports the method's alignment with sustainable chemistry practices, making it a valuable approach for efficient and eco-friendly pharmaceutical synthesis.

Table-I

ENTRY	BASE	EQUIV	SOLVENT	TEMP (°C)	TIME (Hrs)	YIELD (%)
1	DMF	1	Water	2-4	2	50
2	DMF	2	Water	2-4	2	60
3	DMF	3	Water	2-4	2	70
4	DMF	4	Water	2-4	2	78
5	DMF	5	Water	2-4	2	86
6	**DMF**	**6**	**Water**	**2-4**	**2**	**96**
7	DMSO	3	Water	2-4	2	0
8	DMSO	4	Water	2-4	2	0
9	DMSO	5	Water	2-4	2	0
10	NMP	2	Water	2-4	2	30
11	NMP	3	Water	2-4	2	50
12	NMP	4	Water	2-4	2	50
13	DMF	7	Water	2-4	2	91
14	DMF	8	Water	2-4	2	92
15	DMF	10	Water	2-4	2	92

DMF proves to be the most effective base for the condensation reaction, with increasing equivalents leading to higher yields up to **96%.** The use of DMSO and NMP yields significantly lower results, underscoring the superior performance of DMF. This data underscores the importance of choosing the appropriate base and solvent to optimize reaction conditions and enhance overall yield in chemical synthesis.

The table presents a comparative analysis of different bases and solvents in the condensation reaction involving dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), and N-methyl-2-pyrrolidone (NMP) with varying equivalents. The results highlight the efficacy of DMF as a base, showing in **Scheme-I** as significant increase in yield with higher equivalents. Specifically, with 6 equivalents of DMF, the yield reaches 96%, indicating optimal performance under the given conditions.

In contrast, the use of DMSO, irrespective of the equivalent used, results in a yield of 0%, suggesting that DMSO is not effective as a base for this reaction in water. Similarly, NMP shows modest results, with yields ranging from 30% to 50%, which are considerably lower

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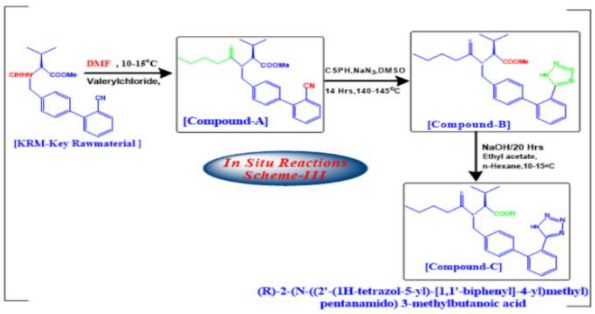
than those achieved with DMF. Notably, increasing the amount of DMF further improves the yield, peaking at 92% with 8 and 10 equivalents. This indicates that DMF enhances both the solubility of reactants and products and the efficiency of the reaction, making it the most effective base for this process.

Scheme-III: (R)-methyl 2-(N-((2'-(1H-tetrazol-5-yl)-[1, 1'-biphenyl]-4-yl) methyl) pentanamido)-3-methylbutanoate (Active compound-C)



The compound (R)-methyl 2-(N-((2'-(1H-tetrazol-5-yl)-[1,1'biphenyl]4yl)methyl)pentanamido)3methylbutanoate, referred to as Active Compound-C, is a complex organic molecule featuring several distinct structural components. This molecule integrates a 1H-tetrazole moiety, which is known for its bioactive properties, with a [1,1'-biphenyl] group. The presence of this biphenyl group in conjunction with the tetrazole enhances the compound's potential for various pharmacological activities. Additionally, the compound includes a pentanamido group linked to a 3-methylbutanoate ester, contributing to its molecular diversity and potentially affecting its pharmacokinetic and pharmacodynamics properties.

The synthesis of Active Compound-C involves intricate chemical transformations, starting with the incorporation of the 1H-tetrazole ring into a biphenyl structure. The subsequent addition of the pentanamido and 3-methylbutanoate groups requires precise control over reaction conditions to ensure high yield and purity. The final structure's complexity suggests a sophisticated approach in its design, aimed at optimizing the compound's interaction with biological targets. This careful design potentially enhances the compound's efficacy as an active pharmaceutical ingredient, demonstrating the importance of strategic molecular modifications in drug development.

Table-II

ENTRY	CATALYST	EQUIV	SOLVENT	TEMP (°C)	TIME (Hrs)	YIELD (%)
1	CC	1	DMSO	140	15	0
2	CC	2	DMF	140	15	0
3	CC	3	DMSO	140	15	0
4	CSPH	4	DMSO	140	15	78
5	CSPH	5	DMF	140	15	86
6	**CSPH**	**4**	**DMSO**	140	15	**95**
7	CAC	3	Water	140	15	0
8	CAC	4	Water	140	15	0
9	CAC	5	Water	140	15	0
10	CSPH	2	Water	140	15	30

CC: Copper (II) chloride ($CuCl_2$):
CSPH: Copper sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$)
CAC: Copper (II) acetate ($Cu(C_2H_3O_2)_2$).

The table shows that CSPH as a catalyst in water or DMSO yields better results than CC or CAC, with the highest yield of 95% achieved in DMSO.

The table details the catalytic performance of various catalysts and solvents in a reaction, with conditions specified in **Scheme II**. Copper chloride (CC) and copper acetate (CAC) were tested as catalysts in different solvents, but neither showed any reaction, yielding 0% under the conditions. Specifically, CC was tested in DMSO and DMF, while CAC was used in water, all resulting in no significant product formation. This suggests that both CC and CAC are ineffective catalysts for this reaction under the tested conditions.

In contrast, copper sulfate pentahydrate (CSPH) demonstrated significant catalytic activity. The reaction with CSPH in dimethyl sulfoxide (DMSO) yielded 78% and increased to 95% with 4 and 5 equivalents, respectively. Notably, CSPH achieved a 95% yield with 4 equivalents of the catalyst in DMSO. In water, CSPH was less effective, producing only a 30% yield with 2 equivalents. This indicates that DMSO provides a more favourable environment for CSPH, enhancing its catalytic efficiency compared to water.

3. Methods

Compound-A preparation:

(R)-Methyl 2-(N-((2'-cyano-[1, 1'-biphenyl]-4-yl) methyl) pentanamido) - 3-methylbutanoate: 0.1955 moles of N-(2-

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cyanobiphenyl-4-yl) methyl-(L)-valine methyl ester hydrochloride was combined with 0.5669 moles of DMF, 450 ml water, and 900 ml toluene in a flask and stirred at 28°C for 25 minutes, then cooled to 0°C. 0.2932 moles of valeryl chloride was added slowly at 0-20°Cover 55 minutes, and the mixture was stirred at 2-4°C for 2 hours. Reaction completion was confirmed by TLC, and the mixture was warmed to 28°C. After adding 450 ml water and stirring for 20 minutes, the organic layer was separated, washed with sodium bicarbonate solution and water, and then concentrated under reduced pressure at 60-68°C to yield the compound with 96% yield and 99.11% purity by HPLC.

Characterization of (R)-Methyl 2-(N-((2'-cyano-[1, 1'-biphenyl]-4-yl) methyl) pentanamido) - 3-methylbutanoate [Compound-A]:

Syrupy mass, Yield: 95%. **MS**: m/z: 407.3, 406.2, 393.1, 375.2, 323.3, 216.1, 192.4, 130.2 and 102.2. **IR data (KBr, ν/cm^{-1}):** 3063, 3029, 2960, 2932, 2873, 2734, 2224, 1943, 1740, 1654, 1597, 1517, 1407, 1168,974, 887,765. **^{1}H-NMR (400 MHz, CDCl$_3$):** δ7.75 (m,2H), δ7.65 (m,1H), δ7.5 (m,2H), δ7.3 (m,2H),7.18 (m, 1H), 4.7 (s, 2H), 4.30 (m, 1H), 3.75 (s, 3H), 3.4 (m, 1H), 2.33 (t, 2H), 1.60 (m, 2H), 1.35 (m, 2H),0.88(t, 3H). 0.95 (d, 3H) 0.90 (d, 3H). This research developed a tetrazole formation reaction using CSPH as a catalyst and DMF as the solvent, achieving the desired yield and conversion. However, DMF is not green due to its toxicity, environmental persistence, and safety hazards, making it incompatible with green chemistry principles that favour safer, more sustainable solvents like water and ethanol.

Compound –B: Synthesis of (R)-methyl 2-(N-((2'-(1H-tetrazol-5-yl)-[1, 1'-biphenyl]-4-yl)methyl) pentanamido)-3-methylbutanoate.

A mixture of DMSO (510 ml), N-[(2′-cyanobiphenyl-4-yl)-methyl]-N-valeryl-(L)-valine methyl ester (0.1819 moles), Copper (II) sulfate pentahydrate (0.918 moles), and sodium azide (0.918 moles) was refluxed for 14-15 hours, then cooled to 30°C. Sodium hydroxide (1.80 moles) in water (1190 ml) was added and stirred for 13 hours. After separating the aqueous layer, it was washed with toluene and

Dichloromethane, and pH was adjusted to 6.75 with acetic acid, then to pH 5 and extracted with dichloromethane. The organic layers were washed, concentrated, treated with cyclohexane, and the residue was filtered, washed, and dried, yielding 96% of solid product with 99.64% purity by HPLC.

Characterization of (R)-methyl 2-(N-((2'-(1H-tetrazol-5-yl)-[1, 1'-biphenyl]-4-yl) methyl) pentanamido)-3-methylbutanoate.

[Compound-B] : Off white solid, Yield: 96% ,MS : m/z : 450.25, 449.2, 434.1, 418.2, 334.1.1H- NMR (400 MHz, CDCl3): δ7.65 (m,2H), δ7.2 (m,2H), δ7.15 (m,2H), δ7.1 (m,2H), 4.8 (d,2H), 4.5 (s, 2H), 3.30 (s, 3H), 3.25 (m, 1H), 2.1 (t, 2H), 1.6 (m, 2H), 1.35 (m, 2H), 1.0 (t, 3H),0.91(d, 3H), 0.90 (d,3H). After the condensation and tetrazole formation reactions, base hydrolysis was used to convert functional groups into more desirable forms. The compound was then purified by precipitation, where it was separated as a solid from the reaction mixture using a precipitating agent. All steps—condensation, synthesis, and purification—were conducted in a single reaction cycle, optimizing resource use and eliminating intermediate purification steps.

Scheme-III: (R)-methyl 2-(N-((2'-(1H-tetrazol-5-yl)-[1, 1'-biphenyl]-4-yl) methyl) pentanamido)-3-methylbutanoate (Active compound-C)

70 g (0.1955 moles) of N-(2-cyanobiphenyl-4-yl) methyl-(L)-valine methyl ester hydrochloride was reacted with DMF, water, and cyclohexane, cooled, and then treated with (0.3925 moles) of valeryl chloride. After stirring and confirming reaction completion by TLC, the mixture was processed through for tetrazole formation i.e. 0.4991 moles of CSPH & 0.4911 moles of sodium azide maintain 14-15 hrs and confirming reaction completion by TLC. The mixture was cooled to room temperature, treated with sodium hydroxide, and adjusted to specific pH levels with acetic acid. Subsequent extractions and washes with cyclohexane, chloroform, and sodium chloride solution were performed. The organic layer was concentrated, and ethyl acetate was added, treated with activated charcoal, and filtered. The filtrate was cooled and the solid was filtered, washed, and dried at 30-35^{o}C for 14 hrs to obtain 79% yield (98grams) (of the desired compound with (99.86% purity by HPLC).

Characterization of (R)-methyl 2-(N-((2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl) pentanamido)-3-methylbutanoate (Final active compound): white solid, Yield: 97%

MS: m/z : 451.2, 450.5, 449.2, 436.4.**IR data (KBr, ν/cm^{-1}):** 3063, 2745, 2614, 1935, 1513, 1390, 1353, 1240, 1164, 1065, 977, 898,885.**^{1}H- NMR (400 MHz, CDCl$_3$):** δ8.05 (d,2H), δ7.5 (m,2H), δ7.35 (d,2H), δ7.19 (m,2H), 5.0 (s,2H), 4.55 (d, 1H), 4.03(s, 3H), 3.45 (m, 1H), 2.8 (bs, 1H), 2.45 (t, 2H), 1.75 (m, 2H), 1.45 (m, 2H),1.0(t, 3H), 0.90 (d,6H).**^{13}C-NMR (101 MHz, DMSO-d$_6$):** δ 177,175, 163,135, 129,128, 127, 75, 57, 51, 35, 28, 27, 23, 19, 14.

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4. Results

This study highlights a significant advancement in the synthesis of 5-substituted 1H-tetrazoles, employing copper sulfate pentahydrate (CSPH) as a catalyst (Scheme II). CSPH plays a crucial role in activating the formation of copper azide, which enhances the selectivity of the [3+2] cycloaddition reaction with nitriles. This leads to high conversion rates of tetrazoles, showcasing the efficiency and effectiveness of this method. One of the key features of this research is the development of a robust, one-pot protocol that uses dimethyl sulfoxide (DMSO) as a solvent. This innovative approach significantly improves reaction efficiency while avoiding the use of toxic hydrazoic acid, making the process safer and more environmentally friendly. The method accommodates a variety of substituents, demonstrating versatility and yielding superior results. Additionally, the simplicity of the work-up procedures adds to the practicality of this method, making it highly attractive for synthetic applications.

Furthermore, the study explores the use of dimethylformamide (DMF) as a base to facilitate smooth condensations **(Scheme I).** The incorporation of DMF enhances the efficiency and yield of the reactions, contributing to the overall robustness of the synthetic methodology. This approach allows for the efficient synthesis of complex molecules with minimal by-products, underscoring its applicability in pharmaceutical synthesis.

In addition to these advancements, the research delves into the in situ synthesis of active pharmaceutical ingredients (APIs) (Scheme III). This method achieves near-quantitative yields with comprehensive structural characterization, highlighting its potential for scalable applications. The ability to produce APIs in situ not only streamlines the manufacturing process but also aligns with green chemistry principles by minimizing waste and reducing the need for hazardous reagents.

5. Discussion

This study underscores the potential for scalable, green chemistry solutions in pharmaceutical development. The findings emphasize the need for continued innovation in eco-friendly synthetic methodologies. By integrating sustainable practices with high-efficiency protocols, this research paves the way for the development of greener and more efficient pharmaceutical manufacturing processes. Overall, the study's findings contribute significantly to the field of green chemistry, promoting the advancement of environmentally responsible synthetic techniques. The innovative use of CSPH as a catalyst, combined with the adoption of safer solvents and bases, sets a new standard for sustainable chemical synthesis. This research not only addresses current environmental concerns but also opens up new avenues for future studies aimed at developing even more sustainable and efficient synthetic methods.

SUMMARY AND CONCLUSION

In summary, our research introduced a novel synthesis route for valaryl chloride and utilized a copper (II) complex with a tetradentate ligand to efficiently form 1H-tetrazoles via [3+2]-cycloaddition under mild conditions. This method, outlined in **Scheme-I** and **Scheme-II,** employs eco-friendly solvents and non-toxic reagents, advancing green chemistry principles. The use of in situ reactions and innovative catalysts demonstrates significant improvements in efficiency, sustainability, and scalability for the development of active pharmaceutical ingredients (APIs). These findings emphasize the effectiveness of new synthetic pathways and highlight the ongoing need for research in sustainable pharmaceutical manufacturing.

DECLARATION OF COMPETING INTEREST

All authors declare no conflicts of interest or competing financial interests.

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