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Green Synthesis of Dapsone: An Eco-Friendly Approach for the Synthesis of 4,4'-Diaminodiphenyl Sulfone

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Abstract: *Dapsone (4,4'-diaminodiphenyl sulfone) is an important sulfone-based antibacterial and anti-inflammatory drug widely used in the treatment of leprosy, dermatitis herpetiformis, and several dermatological disorders. Conventional synthetic methods for dapsone preparation often involve hazardous reagents, toxic solvents, harsh reaction conditions, and environmentally unfavorable processes. Therefore, the development of sustainable and eco-friendly synthetic methodologies has gained considerable importance in pharmaceutical chemistry.*

The present study focuses on the development of an environmentally benign synthetic route for dapsone preparation under mild and sustainable reaction conditions. The synthesis involved condensation of 4-aminobenzenethiol with 4-chloronitrobenzene to form a diphenyl sulfide intermediate, followed by oxidation and subsequent reduction to obtain dapsone. Green chemistry principles were incorporated throughout the synthesis by employing mild reaction temperatures, sonochemical methods, reduced solvent usage, and environmentally safer oxidizing systems.

Thin Layer Chromatography (TLC) was used to monitor the progress of reactions and to evaluate the purity of synthesized intermediates and final products. The synthesized compounds were characterized using FTIR spectroscopy and Nuclear Magnetic Resonance (NMR) spectroscopy. FTIR analysis confirmed the presence of aromatic amine groups, sulfone functionality, and aromatic ring systems, while NMR studies supported successful synthesis of dapsone through characteristic aromatic proton and amino group signals.

The developed methodology demonstrated high reaction efficiency, simple purification procedures, mild reaction conditions, and environmentally sustainable synthesis. Overall, the study highlights the importance of green chemistry in pharmaceutical synthesis and demonstrates an efficient and eco-friendly route for dapsone preparation.

Keywords: Dapsone, green synthesis, sulfone compounds, medicinal chemistry, eco-friendly synthesis, FTIR, NMR spectroscopy, sonochemistry.

I. INTRODUCTION

Sulfone derivatives represent an important class of organic compounds widely used in medicinal chemistry, pharmaceutical industries, and antibacterial therapy because of their diverse biological activities. Sulfone-containing

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drugs exhibit significant antibacterial activity, anti-inflammatory properties, and immunomodulatory effects, making them highly valuable in modern therapeutics. Among these compounds, dapsone is one of the most important sulfone-based drugs widely utilized in the treatment of various infectious and inflammatory diseases.

Dapsone is chemically known as 4,4'\text{-}Diaminodiphenyl\ Sulfone and possesses the molecular formula Structurally, dapsone contains two aromatic amino groups attached to benzene rings along with a central sulfone functional group, which contributes significantly to its pharmacological activity. Due to these structural features, dapsone exhibits excellent antibacterial and anti-inflammatory properties.

Medicinally, dapsone is widely used in the treatment of leprosy, dermatitis herpetiformis, pneumocystis pneumonia, inflammatory skin disorders, and several autoimmune diseases. Its antibacterial activity mainly arises from inhibition of bacterial folic acid synthesis through competition with para-aminobenzoic acid (PABA), thereby interfering with essential metabolic pathways in microorganisms.

Leprosy, also known as Hansen's disease, is caused by *Mycobacterium leprae* and primarily affects the skin, peripheral nerves, eyes, and mucous membranes. Dapsone forms an essential component of the World Health Organization (WHO) multidrug therapy regimen, where it is administered in combination with rifampicin and clofazimine for effective treatment of leprosy.

In recent years, green chemistry approaches have gained considerable importance in pharmaceutical synthesis due to increasing environmental concerns. Conventional pharmaceutical synthesis often involves toxic reagents, hazardous solvents, harsh reaction conditions, and high energy consumption, which may lead to environmental pollution and safety hazards. Green synthesis aims to reduce waste generation, minimize environmental pollution, improve atom economy, and develop sustainable chemical processes. Therefore, eco-friendly synthetic methodologies for important pharmaceutical compounds such as dapsone are highly desirable in modern medicinal and industrial chemistry.

II. OBJECTIVES OF THE STUDY

Primary Objectives

- To synthesize dapsone using eco-friendly reaction conditions.
- To develop a sustainable pharmaceutical synthetic route.
- To characterize synthesized compounds using spectroscopic methods.

Secondary Objectives

- To reduce hazardous reagent usage.
- To improve reaction efficiency.
- To utilize sonochemical and green chemistry approaches.

Step I: Formation of Diphenyl Sulfide Intermediate

The first step in the synthesis involved the reaction between 4-aminobenzenethiol and 4-chloronitrobenzene to produce the diphenyl sulfide intermediate, namely 4\text{-}(4\text{-}Nitrophenylsulfanyl)\text{-}phenylamine. The reaction was carried out using tetrabutyl ammonium chloride as a phase transfer catalyst and sodium hydroxide as the base in toluene solvent. The reaction mixture was maintained at 85°C and continuously stirred for about 2 hours. The reaction

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proceeds through a nucleophilic aromatic substitution mechanism involving replacement of the chlorine atom by the thiol group, resulting in the formation of a diphenyl sulfide linkage.

Step II: Oxidation of Diphenyl Sulfide

The synthesized diphenyl sulfide intermediate was subsequently oxidized using an environmentally friendly oxidizing system consisting of sodium tungstate, hydrogen peroxide, and oxalic acid. The oxidation reaction converted the sulfide linkage into a sulfone group, leading to the formation of 4,4'\text{-}Dinitrodiphenyl\ Sulfone. The reaction was carried out in methanol solvent under reflux conditions at 50°C for approximately 2 hours. The green oxidation process offered several advantages including mild reaction conditions, reduced formation of toxic byproducts, eco-friendly oxidizing reagents, and high oxidation efficiency.

Step III: Reduction of Nitro Group

The nitro groups present in the dinitrodiphenyl sulfone intermediate were reduced using iron powder in the presence of acetic acid, ethanol, and water. The reduction reaction was performed under sonochemical conditions, where ultrasonic irradiation accelerated the reduction process and improved reaction efficiency. Sonication enhanced mass transfer and provided faster conversion of nitro groups into amino groups under comparatively mild reaction conditions.

Step IV: Final Synthesis of Dapsone

In the final step, the reaction mixture containing the reduced intermediate was treated with tin chloride in ethanol solvent. The mixture was subjected to ultrasonic irradiation for about 2 hours to facilitate completion of the reaction and improve product formation. After completion of the reaction, the final product, dapsone, was isolated through crystallization and purified to obtain the desired pharmaceutical compound with good yield and purity.

III. SYNTHETIC SCHEME OF DAPSONE

OBSERVATION TABLE

TLC No.	Mobile Phase	Rf Value	Result
1	Ether : Chloroform (3:2)	0.29	Moderate separation
2	Pet ether : Chloroform (3:2)	0.65	Good separation
3	Ethanol : Chloroform (3:2)	0.90	High mobility
4	Ethanol : Chloroform	0.90	Pure compound observed

FTIR SPECTROSCOPY

Important Functional Groups

Wavenumber (cm^{-1})	Assignment
3300–3500	NH_2 stretching
1580–1620	Aromatic C=C stretching
1300–1150	Sulfone (S=O) stretching
3000–3100	Aromatic C–H stretching

INTERPRETATION OF FTIR SPECTRUM

Important Observations

- NH_2 stretching confirmed amino group formation.
- Strong sulfone peak confirmed oxidation of sulfur atom.
- Aromatic peaks confirmed diphenyl structure.
- Absence of nitro peaks indicated successful reduction.

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NMR SPECTROSCOPY

^{1}H NMR Analysis

Characteristic Signals

Chemical Shift (δ ppm)	Assignment
6.5–8.0	Aromatic protons
4.5–5.5	Amino protons

Interpretation

- Aromatic proton signals confirmed diphenyl framework.
- Amino proton signals confirmed reduction of nitro groups.

^{13}C NMR ANALYSIS

Characteristic Carbon Signals

Chemical Shift (δ ppm)	Assignment
110–140	Aromatic carbons
145–155	Carbon attached to amino groups

Interpretation

- Confirmed aromatic carbon skeleton.
- Supported successful dapsone synthesis.

IV. RESULTS AND DISCUSSION

Efficiency of Green Synthesis

The developed methodology demonstrated:

- mild reaction conditions,
- lower energy consumption,
- reduced environmental pollution,
- and improved safety.

Importance of Sonication

Sonochemical conditions provided:

- faster reaction rate,
- enhanced mass transfer,
- reduced reaction time,
- and improved product formation.

Industrial Significance

The process offers:

- easy purification,
- low-cost reagents,
- scalable synthesis,
- and environmentally sustainable methodology.

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V. ADVANTAGES OF THE PRESENT METHOD

Environmental Advantages

- Eco-friendly reaction conditions
- Reduced hazardous waste
- Safer oxidizing systems
- Lower solvent consumption

Synthetic Advantages

- High product purity
- Mild temperature conditions
- Faster synthesis
- Simple work-up procedure

Industrial Advantages

- Economical process
- Easily available reagents
- Suitable for large-scale synthesis

VI. CONCLUSION

- Dapsone was successfully synthesized using a green and sustainable synthetic methodology.
- The developed process utilized:
  - eco-friendly oxidizing systems,
  - sonochemical techniques,
  - and mild reaction conditions.
- FTIR and NMR analyses confirmed successful synthesis of dapsone.
- TLC studies demonstrated good product purity and reaction completion.
- The methodology showed:
  - improved reaction efficiency,
  - reduced environmental impact,
  - and industrial applicability.
- The study highlights the importance of green chemistry approaches in modern pharmaceutical synthesis and provides an environmentally benign route for the preparation of dapsone.

FUTURE SCOPE

Future studies may focus on:

- microwave-assisted synthesis,
- recyclable nanocatalysts,
- solvent-free synthesis,
- industrial process optimization,
- and biological evaluation of dapsone derivatives.

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