ID 3051

# Synthesis and Separation of Geometrical Isomers of Hydrazone: Towards Effective Antibacterial Agents

Melouki soriya[1], Zeghough djidel [1]

[1] Organic Chemistry Laboratory, Department of Chemistry, Faculty of Science, University of m'sila
*Corresponding author's email: souria28000@gmail.com

**ABSTRACT**

The amine 4,4'-diamino diphenylsulfone is utilized in the synthesis of ethyl pyruvate -4,4' dihydrazonodiphenylsulfone. This process is achieved through the conversion of the amine to its diazonium salts, followed by reduction using tin chloride to produce hydrazine. Hydrazine is then condensed with ethyl pyruvate to yield the desired hydrazone, which is subsequently separated using column chromatography to isolate the following isomers: syn–syn, syn–anti, anti–anti. The physical properties were investigated using spectroscopy methods. The pharmacological study revealed its effectiveness as an antibacterial agent.

**Keywords:** Stereoisomers of aryl dihydrazone, synthesis of aryl hydrazone, separation of hydrazone, cyclization of hydrazone, biological activities of hydrazone

## 1. Introduction

Hydrazone-based compounds, characterized by the azometine -NHN=CH- proton, constitute a significant class of compounds with diverse pharmacological actions [1]. Hydrazones possess an azometine -NHN=CH- proton that has found wide utility in organic synthesis [2-3]. The NH group in hydrazone exhibits higher reactivity compared to the NH group in hydrazide and phenolic OH groups [1]. While traditionally employed for the derivatization and characterization of carbonyl compounds, the N-N linkage in hydrazones has recently gained prominence as a key structural motif in various bioactive agents [3-5]. Numerous hydrazone derivatives have demonstrated various biological activities, including anticonvulsant, antimalarial, analgesic, anti-inflammatory, antiplatelet, antimicrobial, antiviral, antifungal activities [6-9], antihypertensive, anti-tubercular, antiproliferative, antiradical activity [1], and effectiveness against a weak immune system [10]. Notably, some hydrazone derivatives have shown promise in exerting antitumor activities against human lung cancer cells (A549) and human prostate cancer cells (PC-3) [11]. These findings contribute valuable insights into the structure-activity relationship of hydrazone-type compounds and open new perspectives for developing novel potent antioxidants.

## 2. Experimental

### 2.1 Analytical Instruments

The devices used in chemical analysis include Ultraviolet (UV) spectrophotometers, Infrared (IR) spectrophotometers, and Nuclear Magnetic Resonance (NMR) spectrometers.

### 2.2 Preparation Method:2.1 Diazonium Salt Formation (1)

4,4'-diamino diphenylsulfone is combined with hydrochloric acid and water. The mixture is stirred thoroughly while heating. The mixture is then cooled to a temperature of (0 - 4 °C). Gradually, drop by drop, a solution consisting of sodium nitrate dissolved in water is added.

### 2.2.1 Preparation of '4,4'-Dihydrazonodiphenylsulfone (2)

Tin chloride ($SnCl_2.2H_2O$) is combined with concentrated hydrochloric acid (HCl). This mixture is cooled with continuous stirring until reaching (0 - 4 °C). Gradually and slowly, the previously prepared diazonium salt solution is added to the mixture while stirring continuously. The reaction mixture is left in the


DOI: 10.21467/abstracts.169 ISBN: 978-81-970666-4-1 (eBook)

refrigerator overnight at (0 - 4 °C).

### 2.2,2 Preparation of Ethyl Pyruvate-'4,4'-Dihydrazonodiphenylsulfone (3)

To the previously obtained filtrate of hydrazone (2), ethyl pyruvate ($CH_3COCO_2C_2H_5$) dissolved in of isopropanol is added with continuous stirring until a yellow-colored precipitate appears. The formed precipitate is filtered, dried, and weighed.

### 2.3 Isolation of Geometrical Isomers for the Compound: Ethyl Pyruvate-'4,4'-Dihydrazonodiphenylsulfone (3)

Three grams of dihydrazone (3) are placed in a chromatography column with silica gel using a solvent mixture of benzene and acetone in a ratio of 5:1. The subsequent fractions are then separated.
The biological activity of the geometric isomers of hydrazone (3) is assessed using the diffusion method on solid medium. This involves preparing discs from sterile and impregnated filter paper saturated with the prepared hydrazone solutions. The discs are placed on the solid medium by carefully arranging the three studied fractions at different concentrations in methanol as the solvent

## 3. Results and Discussion

The composition and structure of the geometric isomers separated from the dihydrazone (3) were confirmed using infrared (IR) and ultraviolet (UV) spectroscopy, as well as nuclear magnetic resonance (NMR) Table 1.

**Table (1):** *Physical Properties of Geometrical Isomers of Hydrazones (3).*

| **Hydrazone isomers** | ***UV, $\lambda_{max}$ nm in EtOH*** | **$H_o$** d | **$H_m$** D | **N-H** s | ***J, Hz*** | ***IR, $\lambda_{max}$ $cm^{-1}$ in KBr*** | |
|---|---|---|---|---|---|---|---|
| | | | | | | **$NH_{str}$** | **$C=O_{str}$** |
| ***syn-syn*(3)** | 201(4.67)<br>229(374)<br>357(5.01) | 7.81 | 7.19 | 12.19 | $J_{23}$=6.97<br>$J_{Et}$=6.9 | 201(4.67)<br>229(374)<br>357(5.01) | 1677 |
| ***syn-anti*(3)** | 201(4.98)<br>226(4.26)<br>349(5.42) | 7.83<br>7.80 | 7.26<br>7.20 | 12.20<br>7.94 | $J_{23}$=8.7<br>$J_{Et}$=7.2<br>$J_{2'3'}$=8.4 | 201(4.98)<br>226(4.26)<br>349(5.42) | 1647<br>1701 |

### Pharmacological activity

From the obtained results, it was observed that hydrogen bonds play a significant role in pharmacological activity. This is evident in the first harvest, represented by the syn-syn isomer Table2.

**Table (2):** *Biological Activity of Isomers of Hydrazones (3) Against Bacteria.*

| Bacteria | | | | | | | concentration (mg/ml) | substance |
|---|---|---|---|---|---|---|---|---|
| Gram(±) | | Gram(-) | | | Gram(+) | | | |
| Pseudomonas | Acinetobacter | Proteus | Klebsiella | E-coli | Corynebacterium | Staphylococci | | |
| Diameter of the Swept Area mm | | | | | | | | |
| 22 | 20 | 25 | 19 | 22 | 25 | 17 | 0.004 –0.008 | gentamicine |
| 10 | 12 | 18 | 18 | 20 | 24 | 10.5 | 60 | *syn –syn (3)* |
| 21.5 | 13 | 18 | 10 | 15.5 | 17 | 16 | 60 | *syn –anti (3)* |
| 10 | 10 | 16 | 9 | 22 | 19 | 13.5 | 60 | *anti –anti (3)* |

## 4. Conclusions

The appearance of hydrogen bonds in this type of isomers, syn and anti, leads to differences in the physical properties of the geometric isomers of hydrazone (3), such as melting point, UV spectrum, IR spectrum, NMR spectrum, as well as in biological activity against bacteria. It was observed that the biological activity of the -syn syn isomer is greater than that of the other isomers, and that the activity increases with increasing concentration. In general, it can be stated that the dihydrazone prepared exhibits antibacterial biological activity.

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ISBN: 978-81-970666-4-1
Series: AIJR Abstracts
DOI: 10.21467/abstracts.169