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Research Article

A NOVEL SYNTHETIC APPROACH FOR OXAZOLINE AS A CRUCIAL PRECURSOR IN CARVEDILOL DEVELOPMENT

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ABSTRACT

The synthesis of heterocyclic intermediates plays a vital role in the development of pharmacologically active compounds. Oxazolines, five-membered heterocycles containing both nitrogen and oxygen atoms, are of significant interest due to their synthetic versatility, stability, and utility in constructing complex molecular frameworks. The present study focuses on the synthesis of oxazoline derivatives as essential intermediates in the production of anisole-based carvedilol, a widely used non-selective beta-blocker with alpha-1 blocking properties. Oxazolines, known for their versatile reactivity and stability, serve as effective building blocks in pharmaceutical synthesis. In this project, oxazoline compounds were synthesized via cyclization of appropriately substituted amino alcohols with anisole-derived carboxylic acid derivatives under dehydrating conditions. The reaction was optimized for yield, purity, and efficiency, employing green chemistry principles wherever possible. The synthesized oxazoline intermediates were characterized using spectroscopic techniques such as IR, NMR, and mass spectrometry. These intermediates were further used in the stepwise synthesis of carvedilol analogues, highlighting their role in constructing the core structure through regioselective and stereoselective transformations. The study demonstrates the feasibility and efficiency of using oxazoline scaffolds in anisole-based carvedilol synthesis, offering a potential route for improved drug development processes.

KEY WORDS

Cyclodehydration, Acetonitrile, 2-Amino ethanol, Zinc acetate, Calcium carbonate

INTRODUCTION

Carvedilol, a widely used non-selective beta-blocker with alpha-blocking activity, is an essential pharmaceutical agent in the treatment of hypertension and heart failure. This study aims to develop and synthesize oxazoline as a key starting material to produce anisole, an important intermediate in the synthesis of carvedilol. The research focuses on optimizing the reaction conditions for oxazoline synthesis, characterizing the synthesized compound, and evaluating its suitability for further conversion into anisole. This work contributes to an efficient and scalable synthetic pathway for carvedilol production, offering potential improvements in yield and cost-effectiveness. Oxazoline derivatives are valuable heterocyclic compounds with

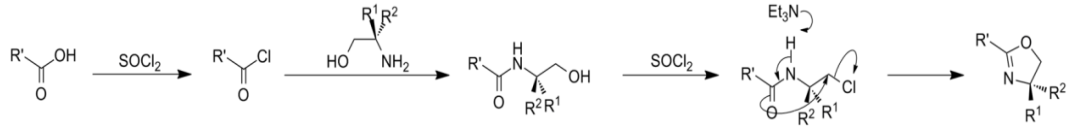
applications in medicinal chemistry, polymer synthesis, and coordination chemistry due to their structural rigidity and bioactive properties. Traditional synthetic approaches often require harsh conditions or expensive reagents. The reaction between acetonitrile and 2-aminoethanol offers a convenient and efficient route to 2-methyl-4, 5dihydro-1, 3-oxazole. This study elucidates the mechanistic details of this transformation, emphasizing the catalytic function of Zn $(OAc)_2$ in promoting ring formation.

SYNTHESIS OF OXAZOLINE

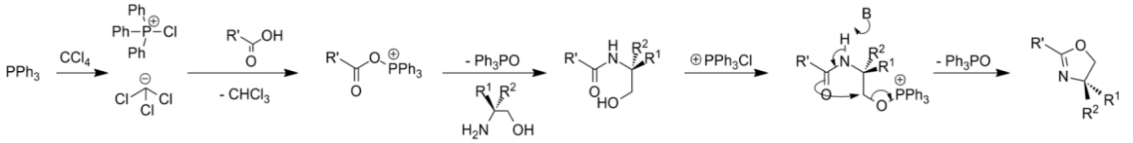
The synthesis of 2-oxazoline rings is well established and in general proceeds via the cyclisation of a 2-amino alcohol (typically obtained by the reduction of an amino acid) with a suitable functional group [1][2][3]. The overall mechanism is usually subject to Baldwin's rules.

From carboxylic acids

The usual route to oxazolines entails reaction of acyl chlorides with 2-amino alcohols. Thionyl chloride is commonly used to generate the acid chloride in situ, care being taken to maintain anhydrous conditions, as oxazolines can be ring-opened by chloride if the imine becomes protonated [4]. The reaction is typically performed at room temperature. If reagents milder than SOCl2 are required, oxalyl chloride can be used [5]. Aminomethyl propanol is a popular precursor amino alcohol. [6][7]

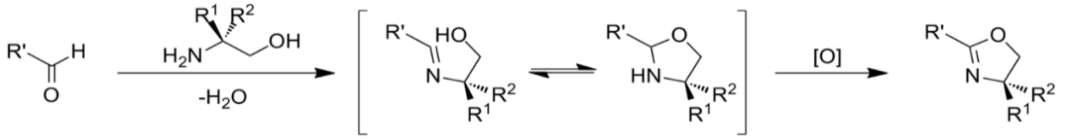


Modification of the Appel reaction allows for the synthesis of oxazoline rings. This method proceeds under relatively mild conditions, however, owing to the large amounts of triphenylphosphine oxide produced, is not ideal for large-scale reactions. The use of this method is becoming less common, due to carbon tetrachloride being restricted under the Montreal protocol.



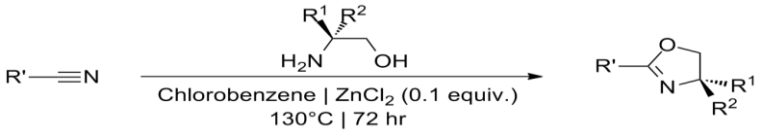
From aldehydes

The cyclisation of an amino alcohol and an aldehyde produces an intermediate oxazolidine which can be converted to an oxazoline by treatment with a halogen-based oxidising agent (e.g. NBS, [8] or iodine [9]); this potentially proceeds via an imidoyl halide. The method has been shown to be effective for a wide range of aromatic and aliphatic aldehydes however electron rich aromatic R groups, such as phenols, are unsuitable as they preferentially undergo rapid electrophilic aromatic halogenation with the oxidising agent.



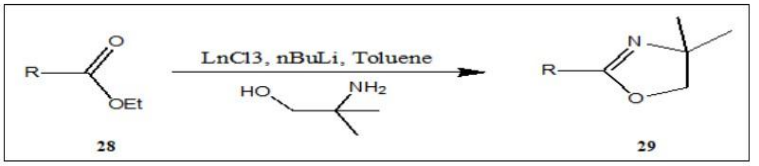
From nitriles

The use of catalytic amounts of $ZnCl_2$ to generate oxazolines from nitriles was first described by Witte and Seeliger [10] [11], and further developed by Bolm *et al* [12]. The reaction requires high temperatures to succeesd and is typically performed in refluxing chlorobenzene under anhydrous conditions. A precise reaction mechanism has never been proposed, although it is likely similar to the Pinner reaction; preceding via an intermediate amidine [13] [14]. Limited research has been done into identifying alternative solvents or catalysts for the reaction.



From Ester

There has been a lot of work reported where oxazoline are prepared from esters. Most commonly esters may get converted into oxazoline by the reaction of esters with the amino alcohols. Zhou et al., [15] were proposed a new method for the synthesis of 2- oxazolines 29 which had a valuable synthetic application for its simplicity, applicability and efficiency. In this method 2-oxazoline synthesized directly from carboxylic esters[25].

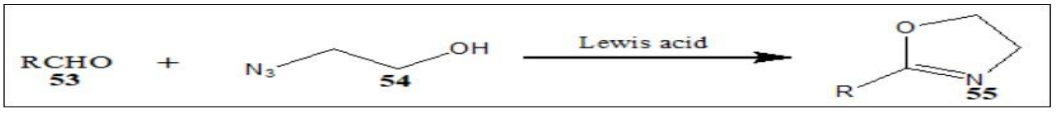


From Amides

A considerable volume of work has been reported where oxazolines are prepared from amides. Some amides cyclize with difficulty, requiring the presence of a dehydrating agent and the use of high temperatures. Others go to the oxazoline with only moderate heat and absence of dehydrating agents. A facile and efficient synthesis of 2-oxazolines 37 from N-(2 hydroxyethyl) amides 36 using triphenylphosphine– 2, 3 - dichloro - 5, 6 - dicyanobenzoquinone (PPh3–DQQ) system was described. The reaction proceeds under neutral and mild conditions and excellent yields were obtained

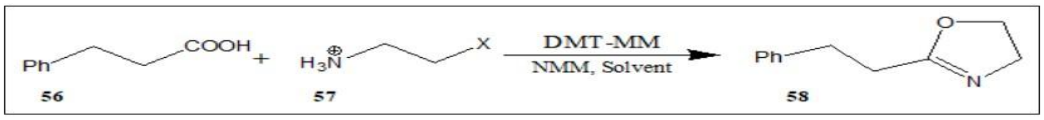
From Azides

The reactions of 1,2- and 1,3- hydroxyalkyl azides 54 and aldehydes 53 in the presence of Lewis acid result in the one-step construction of oxazolines 55 [16]. This reaction involves initial hemiketal formation and subsequent elimination to form an oxenium ion, which is now set up for intramolecular attack by the azide. The resulting intermediate can then form the product via a 1, 2-hydride shift, coupled with N2 loss, followed by proton loss to give the oxazoline product



From Ammonium Salt

Reaction of carboxylic acid 56 and 2-haloethylammonium salts 57 gives 2-oxazolines 58 [17]. The reaction involves dehydrocondensation of carboxylic acids and 2- haloethylammonium salts leading to the formation of N-(b - haloethyl) amides, which then converted into 2oxazolines by the treatment of base. This reaction can proceeds smoothly using 4-(4, 6-dimethoxy-1, 3, 5- triazin- 2- yl) - 4-methylmorpholinium chloride (DMT-MM).



APPLICATIONS

2-oxazoline nucleus has formed many potentially biologically active molecules on modifications. The synthesis, structures and biological activities of oxazoline derivatives have long been focused on research interest of organic chemists in the field of medicine, due to the potential biological activities exhibited by them. Looking into the medicinal importance of oxazoline moiety, it will be worthwhile to synthesize certain newer derivatives of oxazolines and evaluate them for their biological activities.

Anti-microbial: Oxazolines is one of the most important structural units of among all heterocyclic compounds. Many organic chemists have synthesized various antimicrobial derivatives which contain oxazolines ring system.V. Padmavathi et al., [18] have prepared Novel sulfone linked bis (heterocycles) 62 having oxazoline moiety in combination with pyrrole from E aroyl ethene sulfonyl acetic acid methyl ester exploiting ester and olefin functionalities. These compounds exhibited greater antimicrobial activity.

Anti-inflammatory: Oxazolines analogues are very useful in pain control and particularly in the management of oncological pain is the main and important target for the researcher. Oxazoline show good efficiency as chemotherapeutic agent especially as analgesic and antiinflammatory agent. Khanum et al., [19] has been synthesized a series of potential biologically active 2-aryloxy methyl oxazolines 63 from substituted hydroxybenzenes. These synthesized compounds were screened for their anti-inflammatory ulcerogenic, cyclooxygenase activities.

Anti-malarial: Malaria is a very infectious disease, and malaria infection results in over 300 million clinical cases and 1.5–2.7 million deaths worldwide per year. Most of these cases are caused by Plasmodium falciparum, the most virulent human malaria species. 2-oxazolines have long been recognized for their potent biological activity and cost-effective. Oxazoline derivative 69 as a potential anti-malarial agent has been investigated by E. E. Gordey et al [20].

Anti-bacterial: Bacterial infections are one of the major health problems for human mankind. Particularly, the increasing resistance against antibiotics demands the development of conceptually new agents active against bacteria.

Oxazolines and its derivatives act as a good antibacterial agent. Waschinski et al., [21]

investigated selected PMOXDDA polymers with different satellite groups regarding their aggregation behavior in solution and their interactions with liposome as a model for the bacterial phospholipid membrane. The antibacterial activities of these polymer oxazolines were determined with the bacterial strains S. aureus, S. epidermidis, E. coli, and P. aeruginosa. In this experiment N, N Trimethyldodecylammonium chloride was used as a reference.

Anti-tumor: There are many derivatives of oxazolines were reported which shows activity against cancer. Q. Li et al., [22] have been synthesized a series of indole containing oxazolines 75. The compounds exert their anticancer activity through inhibition of tubulin polymerization by binding at the colchicines site. This compound was identified as an orally antimitotic agent active against various cancer cell lines. These optically active 5-aryl oxazolines were synthesized by coupling of the amino alcohol with either the acids or the nitriles. These oxazoline derivatives were evaluated for their antiproliferative activity against the human lung carcinoma cell line NCI-H460 and the MDR positive human colon adenocarcinoma cell line HCT-15 and their anticancer activity of was evaluated in the syngeneic M5076 murine ovarian sarcoma flank tumor model.

Anti-pyretic: Jiang et al., [23] reported a unique optically active spiro [oxazoline-3, 3′- oxindole], a new antipyretic agent. These compounds were synthesized through the organocatalyzed asymmetric synthesis of spirocyclic thiocarbamates via an aldol reaction and the biological activity of spirooxazolines is evaluated on fever by intracerebroventricular (icv) injection of lipopolysaccharide (LPS, a component of the outer membrane of Gram-negative bacteria) using a model of acute neuroinflammation in mice.

Anti-tuberculosis: Tuberculosis (TB) is a very infectious disease resulting in a death every 20 s. Thus, new drugs are urgently needed for the treatment of tuberculosis. The increase in cases of TB/HIV co-infection and the spread of multipledrug resistant TB and extensively drugresistant TB are making matters worse. Moraski et al., [24] reports the structure-activity relationship (SAR) starting from the oxazoline/ oxazole benzyl ester and leading to the identification of imidazo [1, 2-a] pyridines 80 as a new class of potent and metabolically robust antitubercular agents.

CNS Stimulant Activity: Harnden et al., [25] proposed the synthesis of some 5-spirosubstituted 2-amino-2-oxazoline 82 and their effects on the central nervous system. These compounds were synthesized from cyclic ketones involving reduction of the ketone cyanohydrins and reaction of the resultant 2-hydroxyethylamines with CNBr. The effect of CNS activity was evaluated by the observation of albino Swiss-Webster mice for gross changes in behavior. Harnden et al [25] synthesized another CNS stimulant oxazoline moiety 83.

Anti-oxidant: A new class of sulfone linked pyrrolyl oxazolines 84 and thiazolines were synthesized from E-aryl sulfonyl ethene sulfonyl acetic acid methyl ester and studied their antimicrobial and

antioxidant activities 56. The compounds were tested their antioxidant activity by nitric oxide, DPPH methods and reducing power method. These compounds exhibited high antioxidant property in all the three methods at 100 µM concentration. It was observed by Padmaja et al., [26] that the compounds having isoxazole in combination with oxazoline 85 exhibited greater antioxidant activity.

Anti-viral: Berranger et al., [27] has been synthesized a potent antiviral agent carbovir by using chiral oxazoline-N-oxide 76. Peculiarly (-)-Carbovir was reported as a potential agent in treating AIDS 49. And because of this it has been the subject of strong interest and turned out a new kind of (+)-Carbovir whose exhibited antiviral activity. A series of substituted phenyl analogs of 5- [[4-(4, 5-dihydro-2 oxazolyl) phenoxy] alkyl]-3- methylisoxazoles 78 have been synthesized and screened in-vitro against several human rhinovirus (HRV) serotype. This compound is a broad-spectrum Anti picornavirus agent that inhibits replication of 36 out of 45 rhinovirus serotypes at levels ranging from 0.3 to 3.0 µM. And it also prevents paralysis when administered intraperitoneally to mice infected subcutaneously with Echo-9 virus.

The aim of this study is to synthesize oxazoline derivatives as key starting intermediates for the production of anisole-based carvedilol, a clinically important beta-blocker. The research focuses on developing an efficient synthetic route using anisole-derived precursors through cyclodehydration reactions. It also aims to assess the purity, stability, and reactivity of the synthesized compounds using analytical techniques such as TLC, NMR Spectroscopy and Mass spectroscopy.

The overall objective is to establish a reliable, practical, and environmentally conscious synthetic method applicable to pharmaceutical chemistry. Specific goals include reviewing the chemical significance and reactivity of oxazolines, synthesizing oxazoline derivatives from anisole-based precursors using optimized cyclodehydration, and monitoring the reaction progress through TLC. The synthesized compounds will be characterized using Mass and NMR spectroscopy, evaluated for purity, stability, and reactivity, and used to develop a simplified, scalable synthetic route aligned with green chemistry principles.

The study followed a systematic workflow beginning with a literature review to identify suitable synthetic pathways, followed by selection and procurement of required chemicals. Oxazoline derivatives were synthesized and optimized, with reaction progress monitored by TLC and products purified using standard techniques. Characterization was carried out through mass spectroscopy, and results were documented and compared with marketed oxazoline-based drugs. Finally, conclusions were drawn, and future scope for improving the synthesis pathway was proposed.

MATERIALS AND METHODS:

Materials:

3-necked round-bottom flask, vacuum pump, reflux condenser, distillation apparatus, heating mantle, mechanical stirrer, and analytical balance.

Chemical Reagents:

2-Aminoethanol, Acetonitrile, Zinc Acetate, calcium carbonate,

Methods:

All glassware and apparatus were thoroughly washed with distilled water, rinsed with ethanol, and dried in a hot-air oven. Before use, the three-necked round-bottom flask and its components (condenser, mechanical stirrer, and stoppers) were sterilized to ensure the removal of any contaminants. A 250 mL three-necked round-bottom flask was assembled by attaching a reflux condenser to one neck, a mechanical stirrer to the second, and sealing the third with a stopper, and then placed on a heating mantle.

To the flask, 4.91 g of zinc acetate and the required amount of calcium carbonate were added, followed by 95.5 mL of acetonitrile and 119.3 mL of 2-aminoethanol. After initiating the water flow through the condenser, the mechanical stirrer and heating mantle were switched on. The reaction mixture was gradually heated from room temperature (≈20 °C) to 80 °C over four days with continuous stirring. A noticeable color change indicated reaction progress. Upon completion, heating was stopped, and the mixture was distilled to isolate and collect the oxazoline product.

Chemical Reaction:

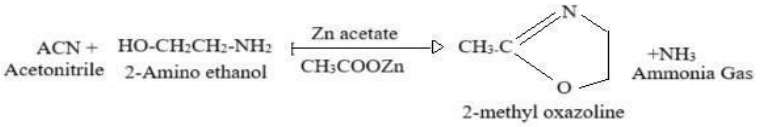


Figure 1: Experimental setup used for the synthesis of Oxazoline

Figure 2: Color change observed indicating the completion of the synthesis reaction

Figure 3: Apparatus used for purification by distillation after synthesis

ANALYTICAL METHODOLOGY

Thin Layer Chromatography (TLC) Analysis of 2-Methyl Oxazoline

The qualitative analysis and preliminary purity assessment of 2-Methyl Oxazoline were carried out using Thin Layer Chromatography (TLC). TLC is a simple, rapid, and cost-effective technique employed for the separation and identification of components in a mixture. It was selected in this case to confirm the presence of the target compound and assess any potential impurities.

Experimental Conditions

Stationary Phase: Pre-coated silica gel G 25261 K05 TLC plate

Mobile Phase Composition: Methanol: Tetrahydrofuran (THF): Liquor Ammonia in the ratio **8:3:1.5**

Sample Concentration: 1.0 mg/mL

Detection Method: UV light at 254 nm

The sample was spotted onto the baseline of the TLC plate using a micropipette and developed in the pre-saturated chromatographic chamber containing the specified mobile phase. After development, the solvent front was immediately marked, and the plate was dried at room temperature. The chromatogram was visualized under UV light (254 nm).

Observation

A single, well-defined spot was observed on the TLC plate with no visible secondary spots, indicating that the compound is relatively pure under the given chromatographic conditions. The spot appeared clearly under UV light, confirming the presence of a conjugated or UVactive compound, consistent with 2-Methyl Oxazoline.

Rf Value Calculation

The Rf value (Retention factor) is a ratio that represents the relative migration of a compound on the TLC plate. It is calculated using the formula:

$$Rf = \frac{\text{Distance travelled by the solute (compound spot)}}{\text{Distance travelled by the solvent front}}$$

Observed Values:

Distance travelled by the compound spot = **3.1 cm**

Distance travelled by the solvent front = **5.0 cm**

$$Rf = \frac{3.1}{5.0} = 0.62$$

The calculated **Rf value was 0.62**, which is reproducible across multiple runs and consistent with literature values for 2-Methyl Oxazoline, thereby supporting its **identity and purity.**

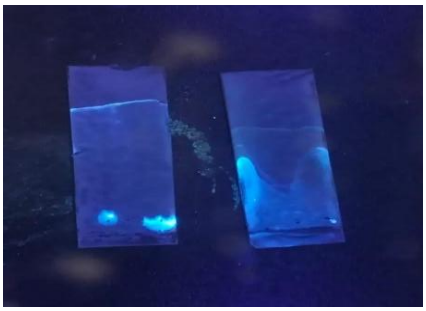


Figure 4: TLC comparison of synthesized compound with standard reference compound

The TLC analysis demonstrated that the synthesized/obtained sample of 2-Methyl Oxazoline is chemically pure under the given conditions, as evidenced by a single spot with a sharp and symmetrical profile and a consistent Rf value. The selected mobile phase composition provided effective separation, and this method can be reliably used for routine quality control and identity confirmation of this compound.

4.1.4 CONCLUSION

4.2 Nuclear Magnetic Resonance (NMR) Spectroscopic Analysis

4.2.1 Sample Details

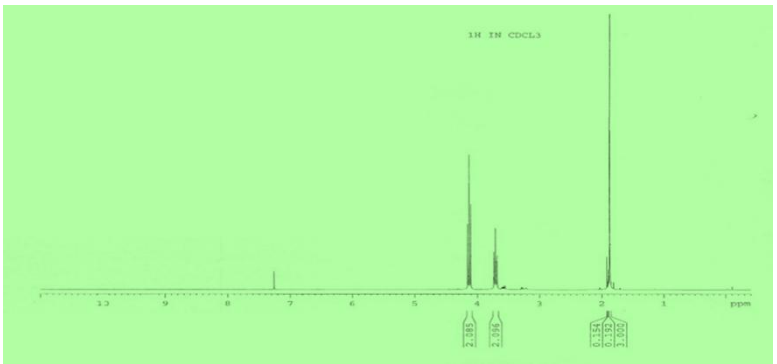
- **Compound Name:** 2-Methyl Oxazoline, C_4H_7NO, M_r = 85.10
- **Solvent:** $CDCl_3$
- **Instrument:** 400 MHz NMR (^1H and ^{13}C)

4.2.2 ^1H NMR (400 MHz, $CDCl_3$)

δ (ppm)	Integration	Multiplicity	Assignment
1.87	3H	Singlet	Methyl (C6)
3.71	2H	Triplet	Methylene at C1
4.13	2H	Triplet	Methylene at C2

- The **singlet at δ 1.87 ppm (3H)** corresponds to the $–CH_3$ group adjacent to nitrogen (C6).
- The **triplet at δ 3.71 ppm (2H)** is assigned to the $–CH_2–$ directly bonded to nitrogen (C1).
- The **triplet at δ 4.13 ppm (2H)** corresponds to the $–CH_2–$ adjacent to oxygen (C2).

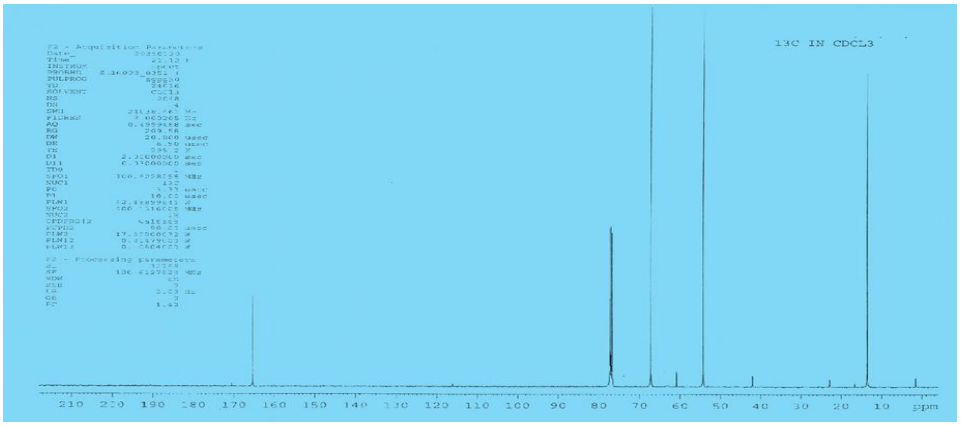
These assignments perfectly align with expected chemical shifts, confirming the molecular structure.



4.2.3 ^{13}C NMR (100 MHz, $CDCl_3$)

δ (ppm)	Integration	Assignment
13.51	1C	Methyl carbon (C6)
54.26	1C	Methylene at C1 (N–CH_2–)
67.17	1C	Methylene at C2 (O–CH_2–)
165.30	1C	Carbonyl carbon (C4, ring)

These resonances are consistent with literature values for 2-methyl-2-oxazoline, confirming structural integrity and purity of the sample.



4.2.4 DISCUSSION

Purity Confirmation:

Both ^{1}H and ^{13}C spectra exhibit clean signals with no extra peaks, aligning with TLC and MS data, supporting the compound's high purity.

Structural Verification:

Observed chemical shifts match literature for 2-methyl-oxazoline confirming ring closure and expected substitution pattern.

Spectral Analysis:

The ^{1}H triplet pattern indicates ideal coupling within the heterocycle.

Downfield carbonyl peak at δ 165.3 ppm is in the expected range for oxazoline rings.

Complementary Evidence:

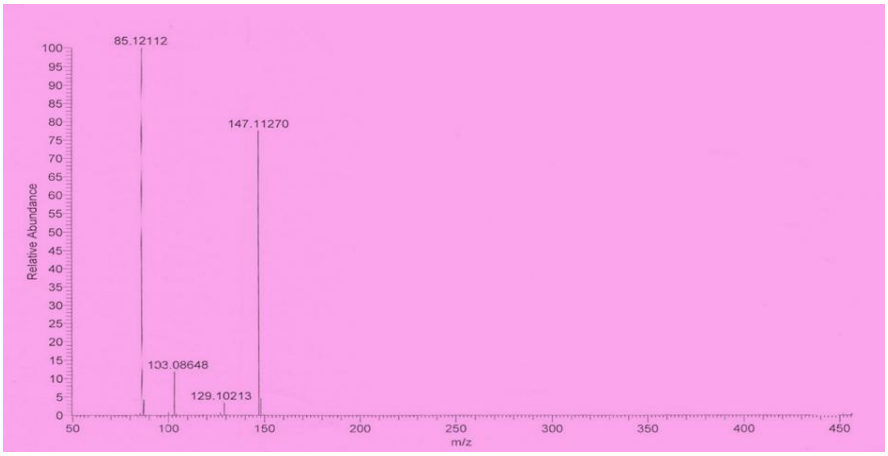
The mass spectrum indicates m/z 85.12 (theoretical 85.10), further validating the identity and consistency of the compound with the proposed structure.

4.3. Mass Spectrometry:

The high-resolution mass spectrum of 2-Methyl Oxazoline displayed major peaks at:

m/z	Intensity (%)	Probable Fragment
85.1211	100	[M]+ (Molecular ion peak, C_4H_7NO)
147.1127	~78	Possible dimer/adduct or fragment
129.1021	~12	Likely fragment (loss of small neutral)
103.0865	~10	Fragment (cleaved side chain)

The m/z 85.12 corresponds closely to the molecular ion peak of 2-Methyl Oxazoline (C_4H_7NO), with a calculated molecular weight of 85.10, confirming the molecular formula and supporting high purity. No unexpected fragment ions were detected, further validating the integrity of the compound.



4.4. CONSOLIDATED RESULTS

TLC Analysis:

Rf = 0.62; single UV-active spot indicates purity and matches expected behavior.

Mass Spectrometry:

Observed m/z = 85.12, in excellent agreement with theoretical mass of 85.10 for C_4H_7NO.

^{1}H & ^{13}C NMR:

Chemical shifts and splitting patterns confirm the presence of one methyl, two methylene groups, and one carbonyl carbon, with no extraneous signals-strongly supporting structural assignment.

CONCLUSION:

The uniformity of TLC, MS, and NMR data confirms the successful synthesis of pure 2-Methyl Oxazoline, consistent with the intended molecular structure. The present study successfully demonstrates the synthesis of oxazoline derivatives as strategic intermediates in the production of anisole-based Carvedilol analogues. The oxazoline ring, due to its chemical stability, ease of functionalization, and ability to act as a directing group, served as a crucial scaffold for introducing the desired anisole moiety in the final β-blocker framework.

The synthetic route employed was efficient, yielding oxazoline intermediates under mild conditions with good purity. These intermediates facilitated regioselective reactions necessary for constructing the Carvedilol pharmacophore, particularly through electrophilic aromatic substitution and subsequent reductive transformations.

Furthermore, the use of oxazoline enabled improved control over substitution patterns, leading to enhanced selectivity and fewer by-products. This approach offers a versatile, modular pathway for the synthesis of Carvedilol and potentially other related β-adrenergic antagonists with substituted aromatic systems.

In conclusion, oxazoline has proven to be a valuable and versatile building block for the targeted synthesis of anisole-based Carvedilol. The strategy developed here provides a foundation for further exploration in the synthesis of novel β-blockers with potentially improved pharmacological profiles.

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