Review

Erlenmeyer Azlactones: Synthesis, Reactions and Biological Activity

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Abstract: This review summarizes results from the literature concerning on synthetic approaches and chemical properties of title compounds as well as their chemical reactions since the azlactone chemistry began in 1893 by Friedrich Gustav Carl Emil Erlenmeyer1 to date are reported. These compounds are important intermediates for the synthesis of a variety of otherwise difficult to obtain synthetically useful and novel heterocyclic systems. The most eye catching features of these structures are their greatest utility resides in pharmaceuticals (analgesic, antibacterial, antifungal, antagonists, anti-inflammatory, anti-microbial, anti-diabetic).

Keywords: Oxazolone; imidazolone; reactions, heterocycles, antimicrobial activity.

1. Introduction

The Erlenmeyer reaction was first described in 1893 by Friedrich Gustav Carl Emil Erlenmeyer1 who condensed benzaldehyde with N-acetyl glycine in the presence of acetic anhydride and sodium acetate. The reaction goes via a Perkin condensation following the initial cyclization of the N-acetyl glycine yielding the so-called Erlenmeyer azlactones.

Erlenmeyer azlactones have been used in a wide variety of reactions as precursors for biologically active peptides, herbicides, fungicides, and as drugs, pesticides and agrochemical intermediates. Oxazol-5-ones inhibit the activity of tyrosinase enzyme with a maximum inhibition by the derivative which bears a cinnamoyl residue at C-4 of oxazolone moiety. Some prepared 3,4-diaryloxazolones showed inhibition of cyclooxygenase-2 (COX-2), in vivo anti-inflammatory and excellent activities of arthritis and hyperalgesia [1-5]. Several imidazolidine derivatives are proved as
insecticides such as imidazolidin-2-one and imidaclopride; herbicides as imazamethabenz-methyl and oxadiargyl and fungicides as iprodione that controlled the brown patch (*Rhizoctonia solani*) [6]. Great fungitoxic effect was exhibited by imidazole derivatives that posse an electron-attracting moiety substituted on the imine nitrogen atom [7-9]. Also, oxazolone and imidazolone derivatives are used as antioxidant and anticorrosive additives for lubricant oils [10-12].

2. Synthesis

The various methods that have been used for the preparation of 2-oxazolin-5-one derivatives are discussed as follows.

2.1. Erlenmeyer Synthesis

In this process, the interaction between carbonyl compounds (aldehydes and ketones) and acylglycines or aroylglycines in the presence of acetic anhydride containing sodium acetate gives the corresponding 4-(alkylidene or arylidene)-2-oxazolin-5-one derivatives (1a-s) as shown in Table 1. The reaction proceeds via the formation of 2-(alkyl or aryl)-5-oxazolones which undergo Perkin condensation with aromatic aldehydes to give the corresponding alkylidene or arylidene oxazolones.

![Reaction Diagram](image)

Table 1: Synthesis of 4-(alkylidene or arylidene)-2-oxazolin-5-one derivatives (1a-s).

<table>
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<th>Comp. No.</th>
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<tr>
<td>a</td>
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<td>b</td>
<td>CH₃</td>
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<tr>
<td>c</td>
<td>CH₃</td>
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<td>CH₃</td>
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Some of the above derivatives have been also prepared using acetic anhydride and alumina as a mild base [31, 32], or calcium acetate under microwave irradiation [33], giving oxazolone (1).

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Treatment of 2,3-dihydro-1,3-diphenyl-1H-pyrazole-4-carbaldehyde with hippuric acid afforded the corresponding (1,3-diphenyl-4-pyrazolin)-4-methylene-2-oxazolin-5-one (2) [34].

When phthalic anhydride was condensed with hippuric acid, 2-phenyl-4-phthalyl-2-oxazolin-5-one (3) was obtained [35].

Condensation of cinnamoylglycine with acetic anhydride and sodium acetate gave a low yield of 2-styryl-4-(α-hydroxyethylidene)-2-oxazolin-5-one (4) [36].

Polyconjugated carbazolyl-oxazolones (6) [37] were synthesized starting from 9-methyl-9H-3-carbazolecarbaldehyde (5) as follow:
Condensation of sodium 2-[4-{2-[4-(dimethylamino)phenyl]-1-diazenyl}benzoylamino]acetate (7) with aromatic aldehydes in the presence of Ph₃P/CCl₄ reagent afforded 4-arylidene-5(4₉H)-oxazolone azo dyes (8a-d) [38].
Cycloalkanones (9) were heated with DMF/DMA giving the intermediate α-enaminoketones (10) which reacted with hippuric acid in the presence of acetic anhydride to give a mixture of pyran-2-one derivatives (11) and oxazolone derivatives (12) [39].

The reaction of N-benzyglycine with o-formyl benzoic acids (13) in presence of acetic anhydride and piperidine as a catalyst afforded 3,5-dioxo-2-phenyl-1,3-dihydropyridine-2,4-[1,3]oxazol-1-ylacetates (14) [40].

Reaction of 1-naphthoyl-glycine (16) with acetic anhydride and triethylorthoformate in ethyl acetate under reflux afforded 4-ethoxymethylene-2-[1]-naphthyl-5(4H) -oxazolone (17) [41].
2-Aryl-4-[4-(1,4,7,10-tetraoxa-13-azacyclopentadecyl)-benzylidene]-5-oxazolone derivatives (19) [42] were prepared by the cyclization of 4-(1,4,7,10-tetraoxa-13-azacyclopentadecyl) benzaldehyde (18) with aroyl glycine derivatives in the presence of acetic anhydride.

The reaction of indole-3-carboxaldehyde (21) with (3-phenyl-propionylamino)-acetic acid (20) in presence of acetic anhydride and calcium acetate afforded the oxazolone derivative (22) [43].

Condensation of 16-formyllambertianic acid methyl ester (23) with hippuric acid in the presence of acetic anhydride and potassium carbonate gave labdanoid oxazol-5(4H)-one (24) in a low yield [44].
Reaction of acylglycines with 4-hydroxybenzaldehyde arenesulfonate esters (25) in presence of acetic anhydride and sodium acetate afforded 2-aryl-4-[4-(arylsulfonyloxy) phenylmethinyl]-4,5-dihydro-5-oxo-1,3-oxazoles (26). The same products were obtained by allowing acylglycines to react with ethyl chloroformate in the presence of triethylamine followed by the reaction with (25) [45-48].

2.2. Bergmann Synthesis

Bergmann and Stern [49] stated that oxazolones can be prepared by the action of acetic anhydride on certain \(\alpha\)-(\(\alpha\)-haloacyl)-amino acids. Thus, refluxing \(N\)-chloroacetyl phenylalanine with acetic anhydride gave 4-benzylidene-2-methyl-2-oxazolin-5-one.
Similarly, 2-benzyl-4-ethoxymethylene-2-oxazolin-5-one (27) was obtained by treatment of N-(α-chlorophenylacetyl)-o-ethylserine with acetic anhydride in pyridine [36].

\[
\begin{align*}
\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}-\text{COOH} & \quad \text{Ac}_2\text{O} \\
\text{NHCOCPh} & \quad \text{Pyridine}
\end{align*}
\]

\[
\text{EtO} \quad \text{CH} \\
\text{27}
\]

2.3. Miscellaneous Methods

Reaction of 4-acetamido-5-phenyl-3-isothiazolidinone-1,1-dioxide (28) with acetic anhydride-pyridine mixture gave the corresponding 4-benzylidene-2-methyl-2-oxazolin-5-one (1) [50].

\[
\begin{align*}
\text{Ph} & \quad \text{NHCOCH}_3 \\
O & \quad \text{Ac}_2\text{O} \\
\text{O} & \quad \text{C}_5\text{H}_5
\end{align*}
\]

\[
\text{28} \quad \text{1}
\]

Coupling of aroylglycines with the appropriate aryldiazonium salts in acetic anhydride containing freshly fused sodium acetate at 0 °C gave 2-aryl-4-arylazo-2-oxazoline-5-ones (29) [51-53].

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{COOH} \\
\text{NHCOAr} & \quad \text{Ar}^1\text{N}=\text{N-Cl} \\
\text{Ac}_2\text{O} & \quad \text{AcONa}
\end{align*}
\]

\[
\text{Ar}
\]

\[
\text{a, Ar}=\text{C}_6\text{H}_5 : \text{Ar}^1=\text{4-OHC}_6\text{H}_5 \\
b, \text{Ar}=\text{4-ClC}_6\text{H}_5 : \text{Ar}^1=\text{4-OHC}_6\text{H}_5 \\
c, \text{Ar}=\text{4-CH}_3\text{C}_6\text{H}_5 : \text{Ar}^1=\text{4-OHC}_6\text{H}_5
\]

The acid catalyzed rearrangement of 3-benzamido-1,4-diphenyl-2-azetidinone (30) gave 4-benzylidene-2-phenyl-2-oxazolin-5-one (1) [54].

\[
\begin{align*}
\text{O} & \quad \text{Ph} \quad \text{C} \quad \text{NH} \\
\text{Ph} & \quad \text{N} \quad \text{Ph} \\
\text{30} & \quad \text{Ph} \quad \text{CH} \quad \text{N} \quad \text{Ph} \\
\text{Ph} & \quad \text{O} \quad \text{Ph}
\end{align*}
\]

\[
\text{Ph} \quad \text{CH} \\
\text{1}
\]
3. Reactions

3.1. Reaction with Acids and Alkalies

Carboxylic acids can undoubtedly cause ring fission of oxazolones even in the absence of water. Carter and Stevens [55] found that, when 4-benzyl-2-phenyl-2-oxazolin-5-one was heated with acetic acid afforded benzoylphenylalanine.

\[
\text{PhH}_2\text{C-} + \text{CH}_2\text{COOH} \rightarrow \text{Ph-CH}_2\text{CH-} + \text{CO} \rightarrow \text{Ph-CH}_2\text{CH-} + \text{CO} \rightarrow \text{Ph-CH}_2\text{CH-} + \text{CO}
\]

The basic hydrolysis of 4-(4-acetoybenzylidine)-2-methyl-5-oxizolone (1) did not yield the expected phenylpyruvic acid, but it gives the enol acetate (31). On the other hand, treatment of (1) with acetic acid afforded enolacetate derivative (32) [56].

\[
\begin{align*}
\text{PhH}_2\text{C-} + \text{COOH} & \rightarrow \text{Ph-CH}_2\text{CH-} + \text{CO} \\
\text{H}_3\text{COCO} & \rightarrow \text{HO} / \text{H}_2\text{O}
\end{align*}
\]

Phenyl pyruvic acid (33) was obtained through a two steps hydrolysis of oxazolones (1L) with aqueous sodium hydroxide followed by aqueous hydrochloric acid [57].

\[
\begin{align*}
\text{Cl-} + \text{H}_{\text{C}} & \rightarrow \text{Cl-} + \text{H} \rightarrow \text{Cl-} + \text{H} \\
\text{1L} & \rightarrow \text{33}
\end{align*}
\]

3.2. Reaction with Amines

3.2.1. With aliphatic and aromatic amines

The 2-oxazolin-5-one derivatives react readily with primary amines than with secondary amines via ring opening of oxazolone at C5 to give the corresponding amides [58]. Thus, reaction of primary aromatic amines with 2-phenyl-4-arylmethylene-2-oxazolin-5-ones (1) leads to ring opening at C5 to give the arylamides of α-carboxamido-β-arylacrylic acids which recyclise to the corresponding 1,2-diaryl-4-arylmethylene-2-imidazolin-5-ones (34) by heating at 200°C under vacuum [59]. It was stated by many investigators that 2-imidazolin-5-one derivatives (34) were also prepared directly by
the reaction of 2-phenyl-4-arylmethylene-2-oxazolin-5-ones with primary aromatic amines in the
presence of acetic acid and sodium acetate [60-66], anhydrous ZnCl$_2$ under fusion [67],
DMF/Me$_3$SiCl [68], or in Pyridine/Zeolite [69-71] under reflux.

Condensation of 2-phenyl-4-arylmethylene-2-oxazolin-5-ones with sulpha drugs at 140°C afforded 2-imidazolin-5-one derivatives (35) [72].

It has been reported that reaction of 4-(ethoxymethylene)-2-phenyl-5-oxazolone (36) with primary aromatic amines in ethanol gave compounds (37) [73,74].
On the other hand, reaction of 2-oxazolin-5-one (36) with diaminomaleonitrile (DAMN) under reflux in alcohol afforded the corresponding propenoates derivatives (38) but at room temperature gave oxazolone (39) which on heating in alcohol afforded (38) [75,76].

![Chemical structure of 2-oxazolin-5-one (36) with pathways to propenoates derivatives (38) and oxazolone (39).]

It was stated by many investigators that anthranilic acid reacts with 2-phenyl-4-arylmethylene-2-oxazolin-5-ones to give the corresponding benzoxazinone derivatives (40) [77-80].

![Chemical structure of anthranilic acid reacting with 2-phenyl-4-arylmethylene-2-oxazolin-5-ones to form benzoxazinone derivatives (40).]

3.2.2. With ammonia

Reaction of (1) with ammonia or ammonium acetate in the presence of potassium carbonate or under microwave irradiation using graphite as a catalyst afforded 2-phenyl-4-arylmethylene-2-imidazolin-5-ones (41) [67,81,82].

![Chemical structure of reaction of (1) with ammonia or ammonium acetate to form 2-phenyl-4-arylmethylene-2-imidazolin-5-ones (41).]

Sawdey has been reported that, treatment of 4-arylazo-2-aryl-2-oxazolin-5-one (29) with ammonia in methanol affects ring opening followed by cyclization to yield 1,5-diaryl-3-carboxamido-(1H)-1,2,4-triazoles (42) [83].
3.2.3. With heterocyclic amines

Treatment of 2-phenyl-4-dichloromethylideneoxazole-5(4H)-one (43) with some heterocyclic amines namely, 2-amino-1,3-thiazole, 2-amino-4-phenyl-1,3-thiazole, 2-amino-4,5-dimethyl-1,3-thiazole, 2-amino-benzothiazole and 2-amino-6-methylbenzothiazole in the presence of THF and triethylamine leads to the formation of enamides (44) and (45) via opening of the oxazole ring. Heating of these enamides with excess morpholine or piperidine in pyridine gave compounds (46) and (47) respectively [84].

Several authors stated that imidazoline derivatives containing sterically hindered phenols possess inhibitors of cyclooxygenase and 5-lipoxygenase [85], α-adrenoblockers [86,87], and anti-hypertensive action [86-89]. So, the reaction of 4-benzylidene-2-methyl oxazol-5-one (1a) with N-acetylhydrazones of 3,5-di(tert-butyl)-4-hydroxybenzaldehyde in acetic acid afforded 2-imidazolin-5-ones (48) in high yield [90].
3.2.4. With amino acids

Azlactones were find diverse applications in the synthesis of aromatic α-amino acids [91-94]. The base catalyzed deprotonation of azlactone and the addition of the resulting anion to aromatic aldehydes leads to the formation of arylidene derivatives (1) which are subsequently transformed into the amino acids (49) in basic medium [95].

\[
\begin{align*}
\text{AcO} & \xrightarrow{\text{Ph}} \text{Ph}^+ \xrightarrow{\text{PhCHO}} \text{Ph}^- \xrightarrow{\text{H}_{2}\text{O}} \text{Ph}^+ \xrightarrow{\text{reduction}} \text{Ar}^- \xrightarrow{\text{OH}} \text{Ar}^+ \xrightarrow{\text{NH}_{3}} \text{Ar}^+ \xrightarrow{\text{CO}_{2}} \text{Ar}^+ \\
\end{align*}
\]

\(N\)-Benzoyl dehydro-3-(3-pyridyl)alanyltryptophan (50) [96] was obtained by condensation of 2-phenyl-4-(3-pyridyliden)-5(4H)-oxazolone with tryptophan in the presence of triethylamine as the condensing agent.
The unsaturated oxazolone were converted into the corresponding dipeptide by two reaction sequences. One is to condense oxazolone with the amino acid ester to form (51) which was hydrolyzed to give (52) [97,98].

\[
\begin{align*}
\text{Ar} & \quad \text{Ph} \\
\text{O} & \quad \text{O} \\
\text{HC} & \quad \text{N} \\
\text{Ar} & \quad \text{H} \\
\text{2} & \quad \text{N} \\
\text{COOR} & \quad \text{1} \\
\end{align*}
\]

On the other hand, reaction of 4-ethoxymethylene-2-(1)-naphthyl-5(4H)-oxazolone (17) with the amino group of peptides gave 2,4-disubstituted oxazolone derivatives (53) and ethylalcohol [99].

\[
\begin{align*}
\text{Naphthyl} & \quad \text{N} \\
\text{O} & \quad \text{Ar} \\
\text{HC} & \quad \text{OC}_{2} \text{H}_{5} \\
\text{53} & \quad \text{EtOH}
\end{align*}
\]

3.2.5. With hydrazines

It has been reported that treatment of 4-arylmethylene-2-phenyl-2-oxazolin-5-one with phenyl hydrazine in acetic acid containing fused sodium acetate gave the corresponding 1,2,4-triazin-6-one derivatives (54) [60,64,100].

\[
\begin{align*}
\text{Ar} & \quad \text{H} \\
\text{O} & \quad \text{N} \\
\text{N} & \quad \text{Ph} \\
\text{54} & \quad \text{PhNH}_{2}
\end{align*}
\]

4-Arylmethylene-2-phenyl-2-oxazolin-5-ones react with hydrazines in alcohol to give the hydrazides (55) [64,100], which undergoes cyclization by heating under reflux with sodium hydroxide to give the corresponding 1,2,4-triazin-6-one derivatives (54) [101,102].
Microwave irradiation has become an important method in organic synthesis that can be applied to a wide range of reactions within short reaction times and with high yields. So, 2-oxazolin-5-ones (56) were irradiated in microwave oven with hydrazine hydrate at 90 W for 10 min. to afford 5-[(6-bromo-4-oxochromen-3-yl)methylene]-3-phenyl-2,5-dihydro-1H-[1,2,4]triazin-6-ones (57) [103].

On the other hand, reaction of 4-benzylidene-2-phenyloxazol-5-one with hydrazine hydrate in pyridine afforded N-amino-2-phenyl-4-benzylidene-1,3-diazol-5-one (58) [104].

Reaction of hydrazine hydrate with 4-arylazo-2-oxazolin-5-ones (29) in the presence of basic reagents yielded 1,5-diaryl-1,2,4-triazole-3-carboxylic acid hydrazides (59) [51] via ring opening followed by cyclization.

1-Acyl-3-hydroxy-1H-pyrazoles (61) were obtained in high yields by the reaction of ethoxymethylene oxazolone (36) with hydrazide derivatives via the intermediate pyrazolone derivative (60). On the other hand, reaction of (36) with two equivalents of an appropriate hydrazine derivative,
the corresponding symmetrically $N,N'$-disubstituted hydrazines (62) together with the oxazoline (63) were obtained. [105,106].

\[ \text{Chemical Structure Image} \]

The chemotherapeutic properties of drugs belonging to the nitrofuran series offer an alternative to antibiotics and antimicrobial [107-109]. So, the reaction of 2-oxazolin-5-one with 5-nitro-2-furohydrazidimide (64) in dioxane afforded 7-benzylidene-5-methyl-2-(5-nitro-2-furyl)-7$H$-imidazo-(3,4-b)(1,2,4)triazole (65) [110].

\[ \text{Chemical Structure Image} \]

3.2.6. With diamines

Many investigators [111-114] stated that fussion of 4-arylmethylene-2-phenyl-2-oxazolin-5-ones with $o$-phenylenediamine at 140°C in the presence of fused sodium acetate gave ($o$-aminophenyl)-4-arylmethylene-2-phenyl-2-imidazolin-5-ones (66) which on refluxing with acetic acid containing sodium acetate afforded benzimidazolo-[2,1-e]-imidazoles (67). On the other hand, when the reaction was carried out with $o$-phenylenediamine in ethanol, the product (68) was obtained. While heating in presence of acetic acid and sodium acetate gave the benzimidazole derivatives (69).
Treatment of 4-arylmethylene-2-phenyl-2-oxazolin-5-one (26) with 2,3-diaminopyridine in ethanol containing fused sodium acetate under reflux gave compound (70). Using acetic acid instead of ethanol yielded 2-[2-[(4-arylsulfonyloxyphenyl)-1-benzoamino] ethen-1-yl] -3H-imidazo (4,5-b) pyridine (71). On the other hand, when the reaction was carried out by fusion with a catalytic amount of fused sodium acetate, 3-amino-2-[4-(4-arylsulfonyloxyphenylmethylene)-5-oxo-2-phenyl imidazolin-1-yl]pyridines (72) were obtained [47].

Condensation of 4-methylbenzylidene-2-phenyl-2-oxazolin-5-one with 1,8-diaminonaphthalene in glacial acetic acid at room temperature yielded a mixture of 2-(4-methylbenzyl)-1H-pyrimidine (73) and 2-phenyl-1H-pyrimidine (74), respectively [115].
It was stated that, 2-alkenyl-4,4-dialkyl-5-oxazolones (75) [116,117] are of special interest for the synthesis of bisazlactones and multiazlactones [118-121] because of their ability to undergo Michael type addition on the vinyl group. They are also key intermediates for a large number of novel monomers and polymers. Their ring opening reaction with primary amines and alcohols has been utilized extensively for the synthesis of acrylamide monomers [116,122,123].

![Chemical structure](image)

3.2.7. With diazocompounds

4-Arylmethylene-2-phenyl-2-oxazolin-5-ones were converted into methyl-α-benzoylamino cinnamates (78) by the action of ethereal diazomethane in methanol. When the reaction was carried out in dry dioxane, the cyclopropane derivatives (79) were formed [36,124,125].

![Chemical structure](image)

Mustafa et al. [125] reported that treatment of 4-ethylidene-2-phenyl-2-oxazolin-5-one (1a) with diazomethane leads to the formation of 4-isopropylidene-2-phenyl-2-oxazolin-5-one (80).
On the other hand, reaction of 4-arylmethylene-2-phenyl-2-oxazolin-5-ones with 1,3-diphenylnitrilimine at room temperature afforded spiro-pyrazolines (81) [126].

4. Biological Activity

2-Oxazolin-5-ones can be considered as semi acid anhydrides which undergo many of the reactions of true acid anhydrides but at a slower rate. This special reactivity allows this class of compounds to be quite useful as serine protease inhibitors, inactivating enzymes such as chymotrypsin [127], human leucocytes elastase [5-9,128,129], porcine pancreatic elastase, cathepsin G [130] and CIr serine protease [131]. The chemical stability and potency of the oxazolones can be turned by choosing substituent which influences the reactivity of the carbonyl by electronic and steric effects.

A variety of 4-(alkoxymethylene)-2-phenyl-5-oxazolone have been designed to inhibit enzymes such as chymotrypsin [132,133], thrombin [134], cathepsin G [128], HSV-1 protease[135], protac R [131], human leukocyte proteinase [136], HLE [137] and pancreatic elastase [127]. 2-Phenyl-4-arylmethylene-2-oxazolin-5-ones act as Cirserine protease inhibitors [131]. Also it converted to the corresponding imidazolones via interaction with 4-amino-1-phenyl-2,3-dimethylpyrazolin-5-one (aminoantipyrine), which acts as non-steroidal anti-inflammatory agents [138]. Also, combination of 2-oxazolin-5-ones with 2-aminothiazole, 2-aminobenzothiazole or 2-aminothiadiazole give substituted imidazolones which act as potent anticonvulsant and enzyme inhibitors [139, 146-147]. On the other hand, it acts as new class of antimitotic, anticancer agents which inhibit tubulin polymerization [140].

Compounds 35 are used for inhibitors HCMV protease, Chymotrypsin and human leukocyte elastase as well as cell culture assay results for antiviral activity [2, 3].
2-Imidazolin-5-ones 48 are useful for the treatment of viral infections, viral protease inhibitors and useful for treatment of infection by CMV, HSV-1, HSV-2 [141].

7-Benzylidene-5-methyl-2-(5-nitro-2-furyl)-7H-imidazo-(3,4-b)(1,2,4)triazole 65 has been synthesized and tested for inhibitory activity against human leukocyte elastase. It was shown activities both in vitro toward human sputum elastase and in vivo in a hemorrhagic assay [142-145].

5. Conclusion

The present survey has clearly demonstrated that azlactones may be successfully used to synthesize a wide variety of heterocycles of academic and pharmaceutical interest. Moreover, in general, the desired compounds may be obtained in a single step with high yield.

References


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