Progress in the Synthesis of Erlenmeyer Azlactone

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***Abstract*- Azlactone is a small and simple molecule having biological activity and high reactivity. Owing to high reactivity, this moiety is transformed into diverse interesting molecules. Generally, this molecule is synthesized by condensation of hippuric acid with benzaldehyde in the presence of the dehydrating agent. Due to its wide applications synthesis of azlactone is a highly explored area in organic synthesis. Therefore, reviewing an article on it will be beneficial for the scientific community. Hence in this article, we have summarized development in the synthesis of azolactone.**

***Keywords*- Erlenmeyer azlactone, hippuric acid, aldehyde, oxazolone, condensation reaction, heterocycle**

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1. INTRODUCTION:

Azlactones are simple molecules with multiple reaction centers (fig.2.1) having biological activity.[1]Initiallyvarious structures have been proposed for oxazolone. In 1893 Rebuffat suggested a three-membered ring structure called lactimide.[2] The same structure was acknowledged by Erlenmeyer in 1893.[3] Later, in 1900 Erlenmeyer rejected this structure in favor of the five-membered ring and named them azlactone.[4]Azlactonesoccur in five isomeric forms, and all of them are identified. All of these isomers are the cyclic esters. Depending on chemical properties, oxazolones are classified into saturated azlactone and unsaturated azlactone.[5] The unsaturated azlactone exists in two tautomeric forms one is real while the other is pseudo.[6]

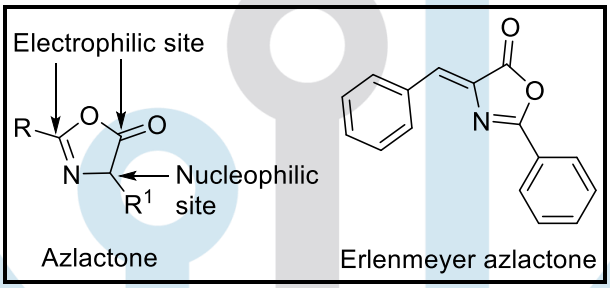


Figure 1: Structure of azlactone

Figure 2: Three and five membered ring structure of azlactone

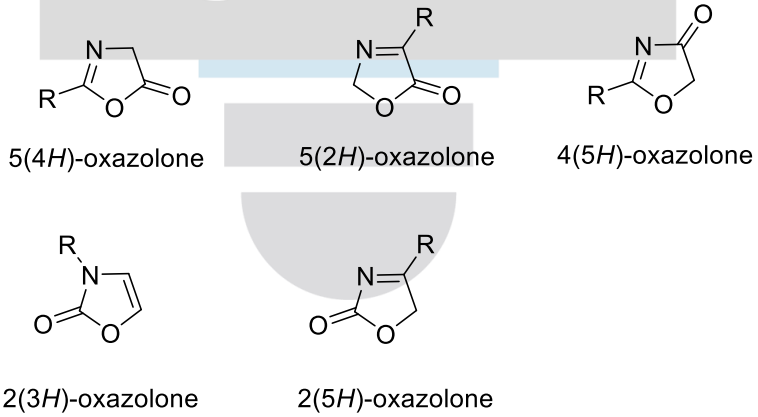


Figure 3: Isomers of oxazolone

Figure 4: Saturated and unsaturated oxazolone

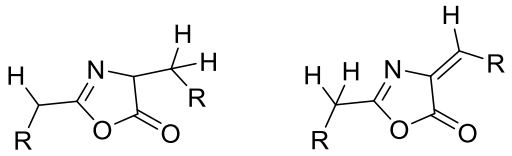


Figure 5: Tautomerism in oxazolone

Azlactone has two, electron deficient and one electron-rich center (Figure 1). Owing to the existence of many reactive centers this molecule can be transformed into to large number of diverse interested molecules which is valuable for biologists and chemists. [7]In 2008 Tepe group established method for the synthesis quaternary substituted *α*-amino acids by using oxazol-5-(4*H*)-ones in stereoselective mode.[8]Additionally, oxazol-5(4*H*)-ones displays extensive range of medicinal properties such as anti-diabetic,[9] immunomodulatory,[10] antifungal,[11] anti-inflammatory,[12] anti-cancer activity,[13] urease inhibition activity,[14]tyrosinase inhibitory activity,[15]Cardioprotective activity,[16]and antibacterial[17] activity. Azlactones also show optical properties which lead to applications in microfabrication, photodynamic therapy, sensing, data storage, and optical imaging.[18] When 6-*β*-naltrexol is covalently linked to a structurally altered form of hydroxybupropion, via a carbonate ester linkage gives a drug CB-NTXOL-BUPOH is a powerful*μ*-opioid receptor antagonist is used in the management of alcohol addiction as well as to help opioid addicts in a drug-free state.[19]Jadomycin B is a natural product having oxazolone skeleton is secreted by Streptomyces venezuelae ISP 5230.[20] It is an antifungal antibiotic having a distinct 8*H*-benzo[b]oxazolo[3,2-f]phenanthridine skeleton.[21]Posizolid(AZD2563) is an oxazolidinone antibiotic active against gram-positive bacteria.[22]

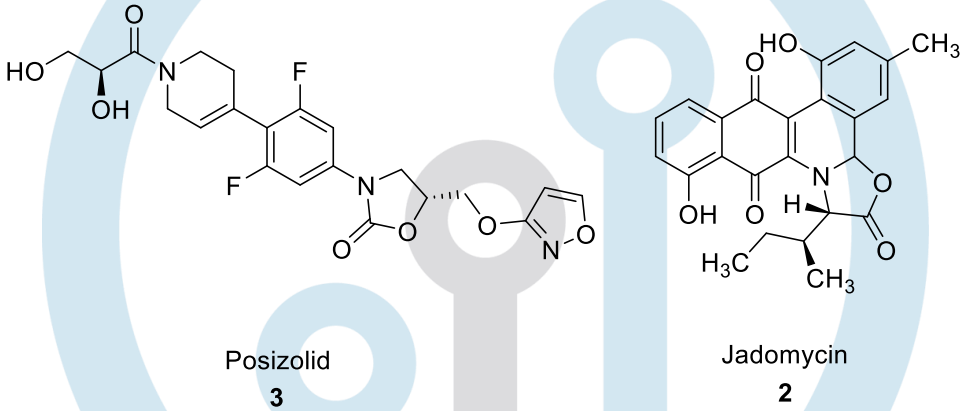
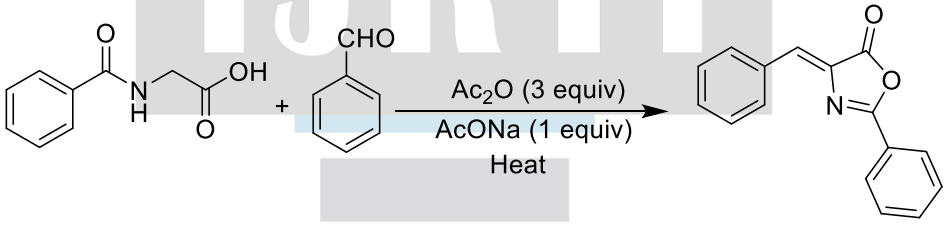


Figure 2.6 Drug molecules containing azolactone ring

2. Methods of synthesis of Erlenmeyer azolactone:

2.1 Synthesis of azlactone by condensation of hippuric acid with benzaldehyde:

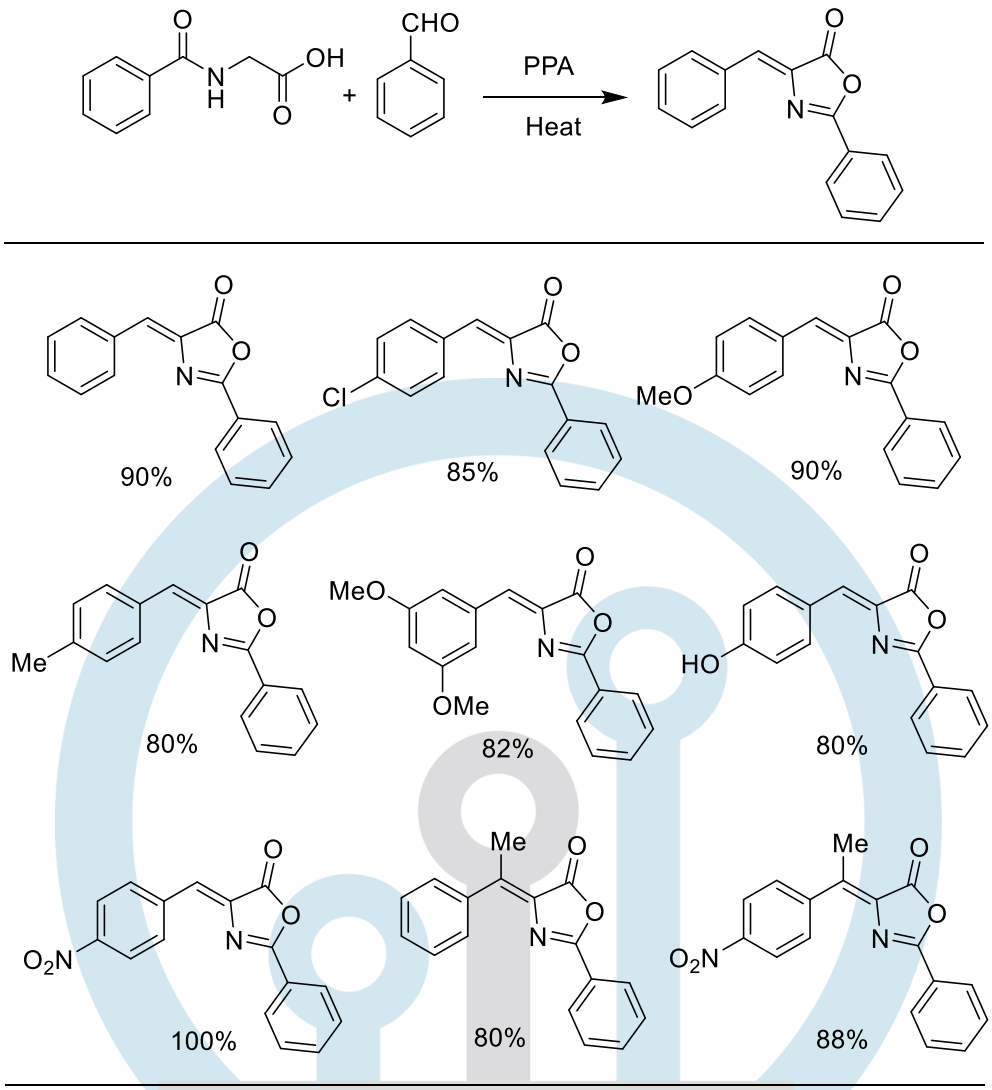
In the original process for the synthesis of azlactone, hippuric acid is condensed with benzaldehyde by using acetic anhydride and sodium acetate.[23]



Scheme 2.1 Condensation of hippuric acid with benzaldehyde by using acetic anhydride

2.2 Condensation of hippuric acid with benzaldehyde by using polyphosphoric acid:

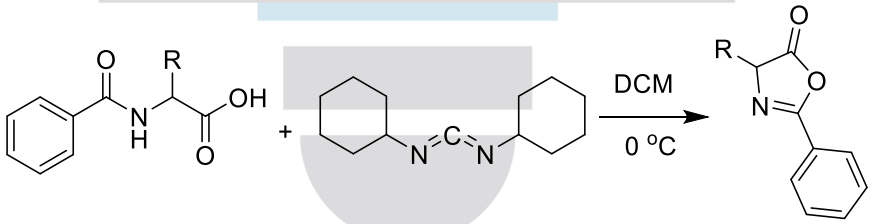
Later in 1976 Rao *et al*. used polyphosphoric acid as a dehydrating agent for the condensation of hippuric acid and benzaldehyde to synthesize azlactone. Furthermore it is already discovered that ketones such as acetone, cyclohexanone, and fluorenone react with hippuric acid to afford corresponding oxazolones but the yields are low. Lure *et al* reported that 3- and 4-nitroacetophenonones react with hippuric acid to give α-arylethylidene azlactones with up to 28% yields. While acetophenone and substituted acetophenones do not react with hippuric acid in the presence of anhydrous potassium carbonate. But all these compounds condense with hippuric acid in the presence of polyphosphoric acid to give α-arylethylidene azlactones in good yields.[24]



Scheme 2.2 Condensation of hippuric acidwith benzaldehyde by using polyphosphoric acid

2.3 Synthesis of optically active oxazolone

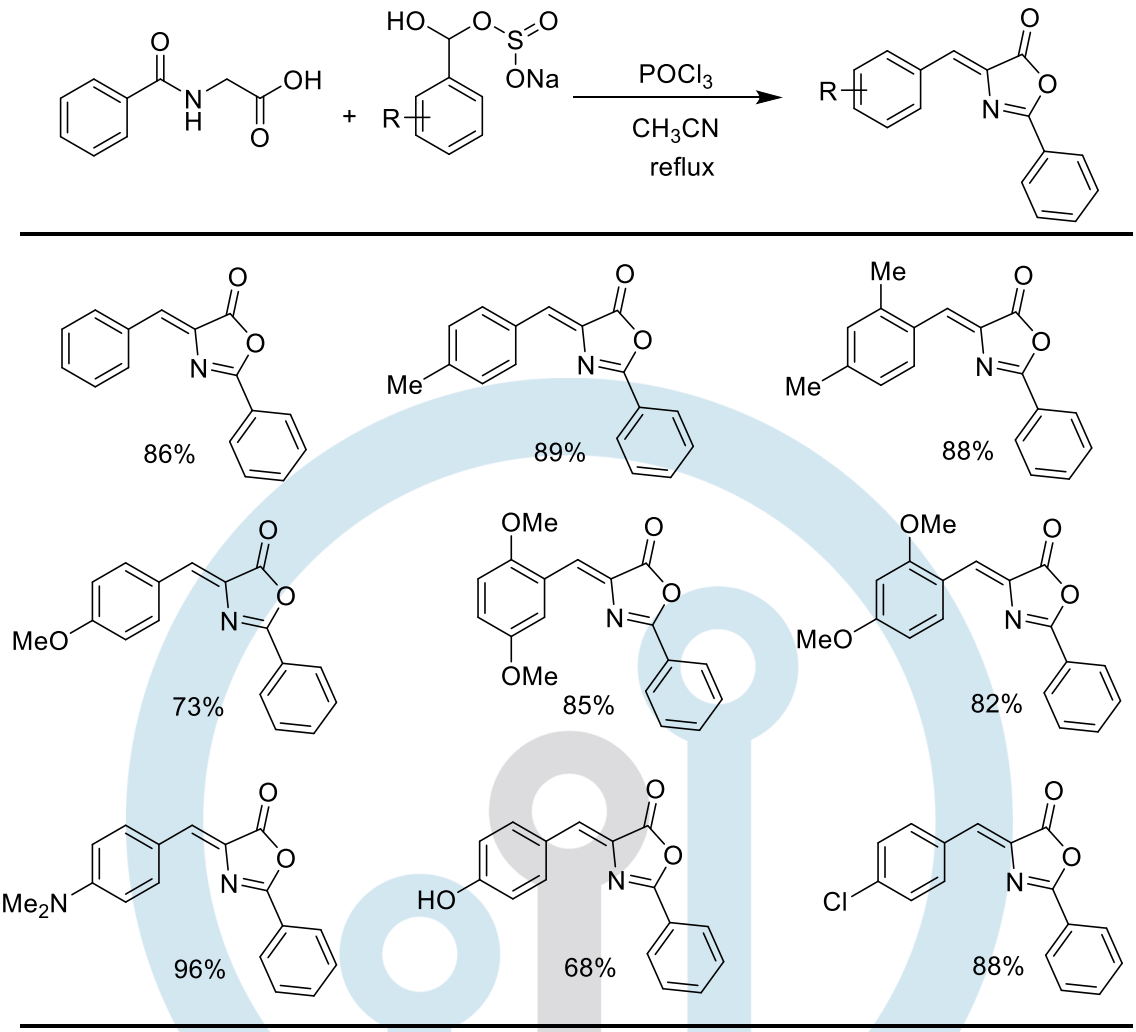
Subsequently, in 1979 Benoiton group developed a method for the synthesis of optically active oxazolone. In this method the solution of amino acid derivative the added solution carbodiimides in DCM at 0°C and stirred it for 15 minutes to give optically active oxazolone. If the solution is stirred for a longer duration(1 h) leads to a racemic mixture of oxazolone.[25]



Scheme 2.3 Synthesis of optically active oxazolone

2.4 By reaction between benzaldehyde bisulfite and hippuric acid:

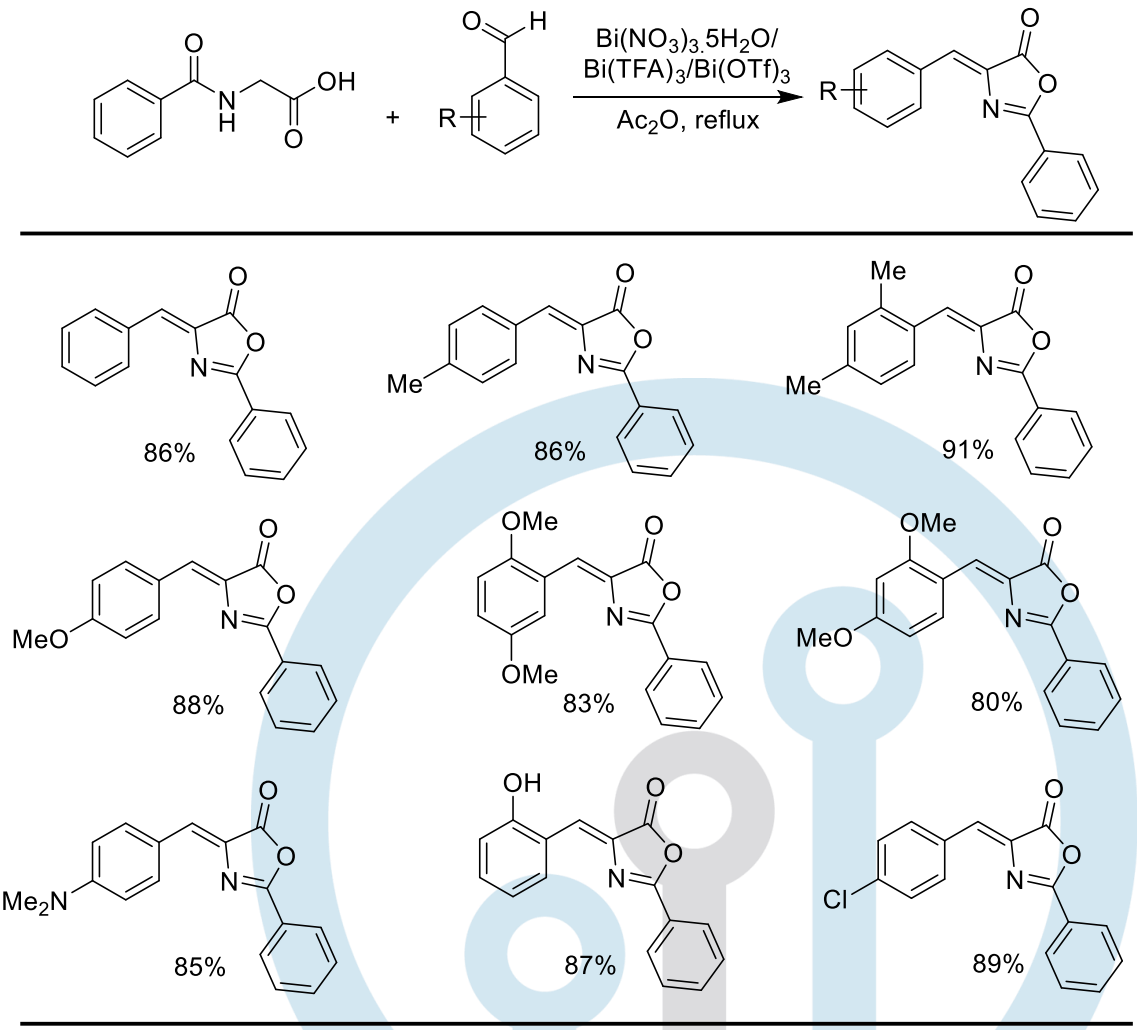
Recently Khosropour *et al.* reported one pot procedure for the synthesis of oxazolone. In this benzaldehyde bisulfite and hippuric acid were refluxed with phosphoryl chloride in acetonitrile which afforded oxazolone in good yield. A highlight of this methodology is the short reaction time and no use of acetic anhydride in the reaction.[26]



Scheme 2.4 Condensation of benzaldehyde bisulfite and hippuric acid

2.5 Condensation of hippuric acid with benzaldehyde by using Bismuth salts:

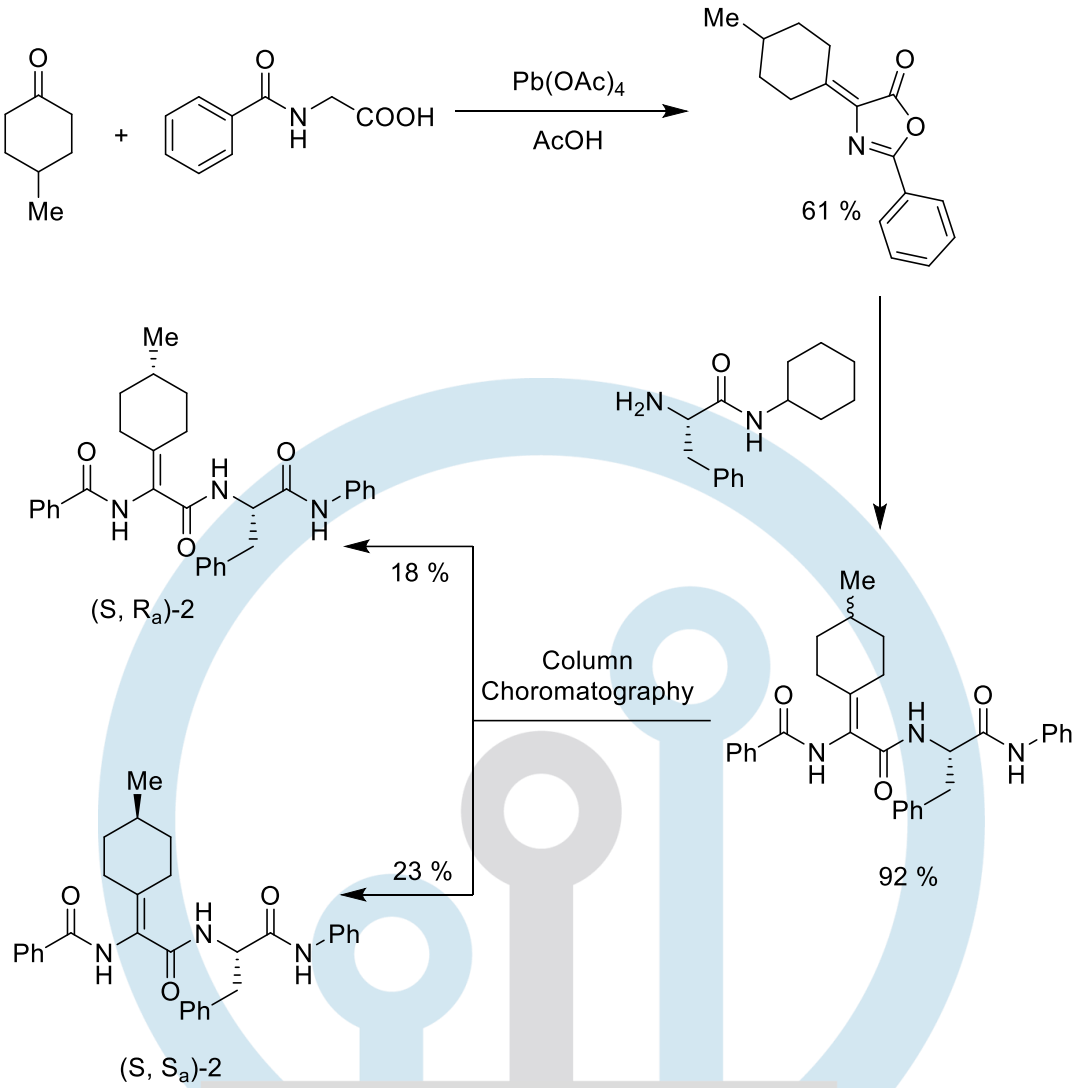
Khodaei and co-workers synthesized azlactone by efficient and chemoselective condensation of aldehyde with hippuric acid in the presence of Bi (III) salts under solvent-free conditions. The advantages of this method are high yield, environmentally friendly, high chemoselectivity, mild reaction conditions, easy experimental procedure, catalytic nature of reagents, low toxicity and cheap availability of Lewis acids, high rate of reaction andmoistureinsensitivereagents.[27]



Scheme 2.5 Condensation of hippuric acid with benzaldehyde by using Bismuth salts

2.6 Condensation of cyclohexanone and hippuric acid in the presence of lead tetraacetate:

Cativiela et al reported Condensation of cyclohexanone and hippuric acid in the presence of lead tetraacetate for the synthesis of azlactone. This azlactone was further converted in to N^2-[N^1-benzoyl-(4-methylcyclohexylidene)glycyl]-*(S)*-phenylalanine cyclohexylamid.[28]



Scheme 2.6 Condensation of cyclohexanone and hippuric acid in the presence of lead tetraacetate

3. Conclusion:

Due to biological and pharmacological activity azlactone is a very important molecule. Therefore, it is highly explored in organic synthesis literature. In this review, we have summarized some methods of very important heterocyclic compound azlactone.

4. Author Information

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5. Notes

The authors declare no competing financial interest

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