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A Heterogeneous approach to synthesis of azlactones

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ABSTRACT: Azlactones are multifunctional compounds which participate in a number of replacement reactions, cycloadditions, dimerisation reactions leading to formation of a variety of intermediates for synthesis of heterocyclic compounds. Interest in the synthesis of Azlactones is due to their unabated diverse bioactivity.This review attempts to present the synthesis of Azlactones and gives a critical and unified account of these in the heterocyclic Chemistry.

KEYWORDS: azlactones, aromatic aldehydes, hippuric acid,cyclodehydration

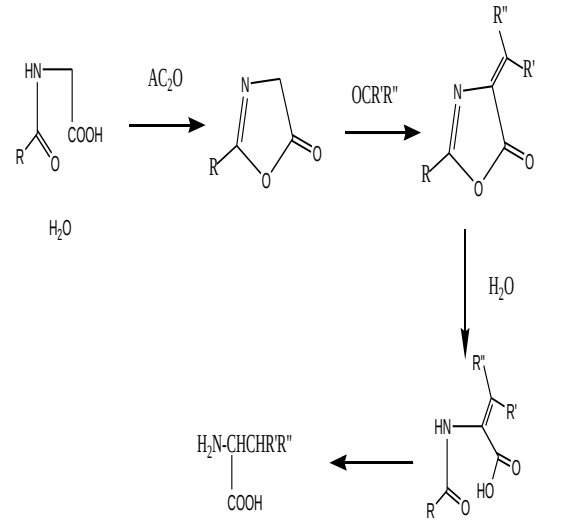
I. INTRODUCTION

These compounds exhibit important biological activities such as antimicrobial[1], antibacterial[2], analgesic[3], antifungal[4],anticancer[5][6], anti-inflammatory[7],neuroleptic[8], sedative[9], antidiabetic[10] and antiobesity[11]. Azlactones are important intermediates in the preparation of several chemicals including Aminoacids[12],peptides[13], some heterocyclic precursors[14] as well as coupling and photosensitive devices for proteins[15].They exhibit promising photophysical and photochemical activities[16][17][18] and as P^H Sensors[19].

Conventional method of synthesis

First Plochl[20] reported the formation by the acetic anhydride mediated condensation of hippuric acid with benzaldehyde. Erlenmeyer established the structure and named it as ‘azlactone’. The Erlenmeyer azlactones are 5 membered heterocyclic compounds containing N and O as heteroatoms.

The Erlenmeyer-Plochl azlactone and amino acid synthesis, named after Friedrich Gustav Carl Emil Erlenmeyer who partly discovered the reaction, is a series of chemical reactions which transform glycine to various other amino acids via an oxazolone and an azlactone.



The routine method for the synthesis of Azlactones is followed from Vogel’s Pratical chemistry

During the past few decades, Many research papers have been published in the area of Erlenmeyer synthesis by using different methods such as usage of catalysts like Al_2O_3,organic bases supportedheteropolyacids[21,22],

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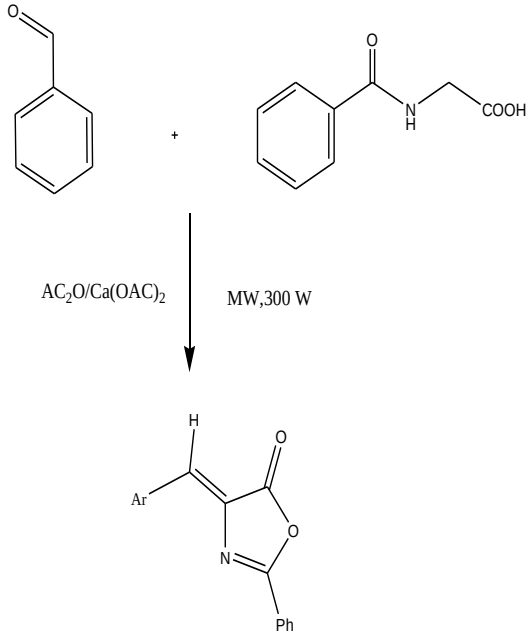
$Yb(OTf)_3$[23]$Ca(OAc)_2$[24],$Bi(OAc)_3$[25],$H_3PW_{12}O_{40}$[26].
The C-2 and C-4 positions of azlactones are crucial for their various biological activities[27].

Non conventional method
The use of nonconventional reaction conditions require a short reaction time compared to conventional heating and easy workup.
Reaction on solid support without using solvent in domestic microwave oven are currently in use for organic chemist to create ecofriendly environment.

Microwave Method
[a] Solid support Erlenmeyer synthesis of azlactones using microwaves
A rapid and ecofriendly procedure for the synthesis of azlactones are reported in dry media using silica gel as a solid support under microwave irradiation.

[b].Eight 4-arylidene-2-phenyl-5(4H)-oxazolones (azlactones) have been prepared via Erlenmeyer synthesis from aromatic aldehydes and hippuric acid using calcium acetate under solvent-free conditions with microwave irradiation.



[c]. Bismuth(III) acetate catalyzes the synthesis of azlactones from aromatic aldehydes in moderate to good yields via the Erlenmeyer synthesis. The relatively low toxicity and low cost of bismuth(III) acetate make this procedure particularly attractive.

[d].A series of 4-arylidene-2-phenyl-5(4)-oxazolones were synthesized from cyclodehydration-condensation of hippuric acid, aromatic aldehydes, and acetic anhydride catalyzed by ytterbium(III) triflate under mild conditions in excellent yields.

[e].Microwave assisted synthesis of azlactone derivatives using 2-aminopyridine functionalised sphere SiO_2 nano particles as a reusable heterogeneous catalyst.

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[f].The Zwitterionic Imidazolium Salt:

First used for Synthesis of 4-arylidene-2-phenyl-5(4H)-oxazolones under Solvent-free conditions

For synthesis of azlactones via Erlenmeyer synthesis, Zwitterionic imidazolium salt was prepared from aromatic aldehydes and hippuric acid under solvent free conditions.

[g].Microwave assisted Erlenmeyer synthesis of Azlactones catalysed by $MgO\text{-}Al_2O_3$ under solvent free conditions.

Synthesis of Azlactones derivatives were carried out successfully from condensation reaction of aldehydes with hippuric acid and acetic anhydride under microwave irradiation using $MgO\text{-}Al_2O_3$ as catalyst which is low toxic in nature and reusable.

Our work involved the synthesis of few condensed heterocyclic compounds from azlactones.

Azlactones(anhydrides of α-acylamino acids) are formed by the condensation of aromatic aldehydes with acyl derivatives of glycine in the presence of acetic anhydride and anhydrous sodium acetate (Erlenmayer azlactone synthesis). Thus benzaldehyde and acetyl or benzoyl glycine yields the azlactone of α-acetamino or α-benzylamino cinnamic acid.

The resulting 4-Benzylidine-2-methyloxazol-5(4H)-one is condensed with 4-nitrobenzene-1,2diamine in 1:2 molar proportion in acetic acid at 1000c temperature for one hour on hot water bath. On cooling and filtering, orange coloured compound is obtained which is recrystallised from ethanol.

[h]. From diazonium salts

Coupling of aroyl glycines with the appropriate aryl diazonium salts at 0ºC gave 2-aryl-4-arylazo-2-oxazoline-5-ones [28-30].

[i] By ionic liquids

Aromatic aldehydes on reaction with hippuric acid in presence of ionic liquid triethylamine hydrogen sulphate to yiled oxazolones with excellent yield and lowest amount of impurities. It was a facile and stereoselective green approach and gave excellent yields.The notable feature of this pathway is that the ionic liquid eliminates the use of acetic anhydride which is carcinogenic. This environment friendly approach enhanced high yield of nearly 95-97%, reducing the production of by products devoid of using exceedingly toxic reagents for the synthesis and more markedly, the Z-enantiomer was obtained[31].

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[j] General method for the preparation of (4Z)-4-(arylidene)-2-(2-hydroxyphenyl)oxazol-5(4H)-ones

A mixture of 1mmol (0.195 gms)of 2-hydroxy hippuric acid,1mmol(0.185gms)of suitable aldehyde,3mmol of acetic anhydride and 1 mmol (0.082gms)of fused anhydrous sodium acetate was heated on an oil bath at 140-150^{0}C for 3-4 Hrs and then cooled.Then 5ml of ethanol is added slowly to the contents of the flask and the mixture is allowed to stand overnight.The compound is filtered under suction,washed with 10ml of ice cold ethanol and then with 10ml of boiling water and air dried and recrystallised from Hexane[32].

Appendix

The most eye catching features of these compounds is there utility in pharmaceutical industry and there is further scope for their exploration.

The present focus is on molecular docking studies which stimulate the molecular recognition process computationally. The Azlactone derivatives bind to DNA by intercalating in between the DNA base pairs. These molecules can be considered as good DNA intercalators.

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