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Azlactones in heterocyclic synthesis: Part-V- Condensation of Azlactones with 4-nitrobenzene-1, 2-diamine

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ABSTRACT

A systematic study of condensation of 4-nitrobenzene-1, 2-diamine with 2-oxazolin-5-ones under milder conditions has been carried out. The structural elucidation of the resulting compounds are determined by IR, ^{1}H-NMR and Mass spectra and the antibacterial activity of products are presented in this paper.

Key words : p-toluene sulphonic acid, 4-nitro- 1,2-diaminobenzene, azlactone (2-oxazolin-5-one),acetamide,anti-microbial screening.

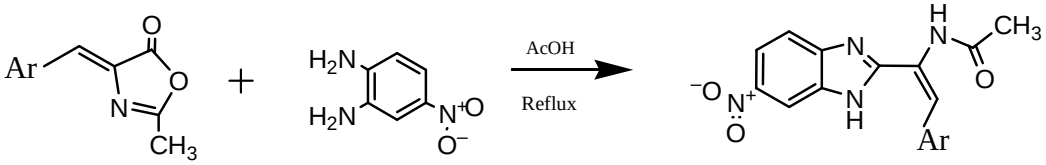
INTRODUCTION

Interest in the chemistry of 2-oxazolin-5-ones (azlactones) is due to their usefulness as intermediates in the synthesis of diverse heterocyclic compounds. 2-oxazolin-5ones (azlactones) are multifunctional compounds and are known to react at C=C, C=N, C=O bonds. These participate in a number of replacement reactions, cycloadditions, other type of reactions as well as dimersation reactions leading to formation of a variety of heterocyclic compounds. Azlactone provides a basic skeleton structure and also is a part of great importance for its drug characteristics. The basic nucleus imidazole emerges from the drug intermediate-azlactone. The azlactones posess oxazolone moiety and known to exhibit antifungal, antibacterial and anti-inflammatory activities.

EXPERIMENTAL SECTION

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.[10]

The resulting 4-Benzylidine-2-methyloxazol-5(4H)-one is condensed with 4-nitrobenzene-1,2-diamine in 1:2 molar proportion in acetic acid at 100^0c temperature for one hour on hot water bath. On cooling and filtering, orange coloured compound is obtained which is recrystallised from ethanol.



I II III

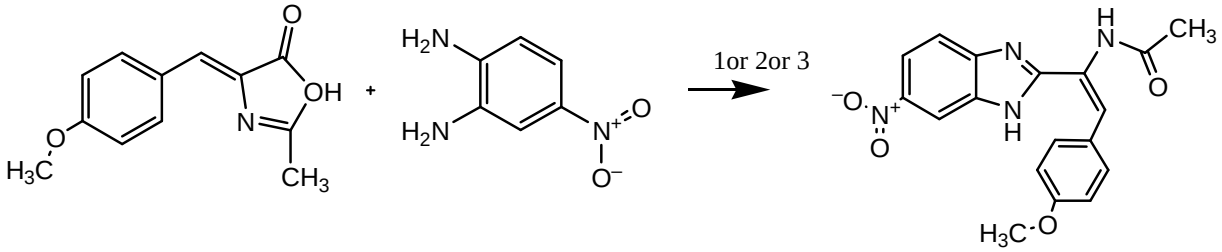
Ar=phenyl,methoxy phenyl,m-nitro phenyl,p-chloro phenyl

The reaction of azlactone (I) with 4-nitrobenzene-1,2-diamine (II) in 1:2 molar proportion in acetic acid at 100^0c temperature for one hour on hot water bath, on cooling orange coloured compound (E)-N-(1-(6-nitro-1H-benzo[d]imidazol-2-yl)-2-phenylvinyl)acetamide (III) is separated which is recrystallised from ethanol showed single spot in TLC.

Yield : 68%; M.P: 178^0c; IR (KBr): 3343cm^{-1},1667 cm^{-1},1519.9 cm^{-1},1336.7 cm^{-1}, 1159 $cm^{-1.}$ ^{1}H-NMR(DMSO) : δ2.6(s,3H),6.1(s,H),6.5(d,3H),7.4(m,5H),8.0(s,H).; EI-MS: 323(M^+), 236.2(56%), 178.2(100%),147.2(38%).

Based on the spectral data the compound is identified as (E)-N-(1-(6-nitro-1H-benzo[d]imidazol-2-yl)-2-phenylvinyl) acetamide (III).

2) Synthesis of 2-(4-methoxyphenyl)-1-(6-nitro-1H-benzo[d]imidazol-2-yl)vinyl)acetamide



IV II V

1= acetic acid ; 2= Ethanol/ p-toluene sulphonic acid, room temp
3= Ethanol/ p-toluene sulphonic acid, reflux

A mixture of 18.6 grams of acetyl glycine, 23ml of p-methoxy benzaldehyde, 9.6 grams of freshly fused anhydrous sodium acetate and 39ml of acetic anhydride in a 500ml RB flask equipped with reflux condenser on a water bath. The reaction mixture is boiled for one hour, cooled and left in a refrigerator overnight.

Condensation of I with 4-nitro-o-phenylene-1,2-diamine in 1:2 molar proportion in acetic acid and reflux on hot water bath for one hour followed by cooling and filteration, orange coloured compound separated which is recrystallised from ethanol (TLC single spot).

Condensation of 4-(4-methoxybenzylidene)-2-methyl-1H-imidazol-5(4H)-one (IV) with 4-nitro-o-phenylene-1,2-diamine and p-toluene sulphonic acid in 1:1:1 molar proportion in ethanol at room temperature for 24 hours and second reaction is condensation of IV with 4-nitro-o-phenylene-1,2-diamine (II) and p-toluene sulphonic acid in 1:1:1 molar proportion in ethanol and reflux on hot water bath for one hour, orange coloured compound is separated for both procedures which are recrystallised from ethanol. The compounds were found to be same as evidenced from T.L.C and spectral studies.

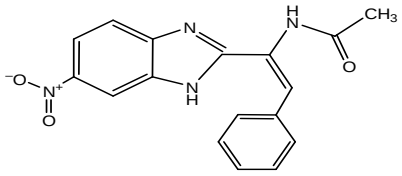
All the other compounds Ar=phenyl,p-chloro phenyl,m-nitro phenyl are condensed with 1,2 diamine to give rise to the product.TLC showed single spot,base don spectral data and anology the compounds are characterized as III.

Spectral Data
IR (KBr): 3351 cm^{-1},1721 cm^{-1},1272 cm^{-1},1590 cm^{-1}; ^{1}H-NMR :δ2.3(s,3H), δ3.8(s,3H), δ6.7(d,H), δ7.1(d,2H),; ($CDCl_3$, DMSO) δ7.2(b,H), δ7.5(s,H),δ7.6(d,2H),δ7.8(d,H), δ 7.9(s,H). EI-MS: M^+ 352 (M^+not recorded), 298(13%),264(23%), 219(30),206(100%),178(72%).

Based on the above spectral data and anology,the compound is identified as (V).

(*E*)-*N*-(2-(4-methoxyphenyl)-1-(6-nitro-1*H*-benzo[*d*]imidazol-2-yl)vinyl)acetamide

A**nti microbial activity of (E)-N-(1-(6-nitro-1H-benzo[d]imidazol-2-yl)-2-phenylvinyl)acetamide**



The development of resistance to existing antibiotics and increasing public concern over environmental pollution and toxicity generated a continuing need for new antibiotic agents. Over the last two decades, both synthetic and plant based products from a variety of sources have been identified and developed in this regard.

EXPERIMENTAL SECTION

The culture of microorganisms used were purchased from commercial source. The organisms included *Escherichia coli,Pseudomonas aeruginosa,Klebsiella pneumonia,Staphylococcus aureus, Bacillus subtilis* for the antimicrobial assays. Cultures of test organisms were maintained on nutrient agar and sub-cultured in petridishes prior testing.

The readymade medium (Hi-media,2.8gms) of nutrient agar was taken which was commercially available,weighed, dissolved in 100ml distilled water. The medium and petridishes were autoclaved at 121^{o}C and 15 psi for 15 min. [11]

Antimicrobial screening:

The (E) – N - (1 - (6 – nitro - 1H – benzo [d] imidazol – 2 – yl) – 2 -phenylvinyl) acetamide under study (1mg/ml)was dissolved in 10ml of aqueous methano l.200µl and 1ml sample was separately mixed with nutrient agar(100ml distilled water). The medium along with sample was poured into petridishes under aseptic conditions in a laminar flow chamber and left to solidify. These petridishes were inoculated with cultures of test organisms and observed after 24hours incubation at 37^{0}C in incubator.

Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia, Staphylococcus aureus, Bacillus subtilis controls were maintained with methanol only.

The sample under study (2mg/ml) was dissolved in 20ml of methanol. 600µl and 3ml sample,800 µl and 4ml of sample was separately mixed with nutrient agar(Hi-media,5.6gms) dissolved in 200ml distilled water. The medium along with sample was poured into petridishes under aseptic conditions in a laminar flow chamber and left to solidify. These petridishes were inoculated with cultures of test organisms and observed after 24 hours incubation at 37^{0}C in incubator. controls were prepared without the sample.

RESULTS AND DISCUSSION

At 200µl concentration,the sample did not inhibit the growth.Instead the organisms survived at this concentration.In case of *Pseudomonas aeruginosa*,a bluish green fluorescence appeared in the entire plate,whereas in control,the colour was localized.The organism may be utilizing this compound as carbon source.However the end product was not confirmed.

600 µl and 800 µl sample were taken and further studies were made based on visual observance.

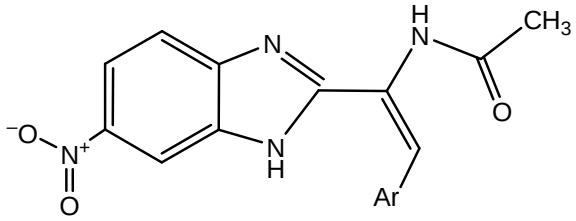
Results of Antimicrobial activity

S.No	Name of Bacteria	600 µl concentration	800 µl concentration	Control without sample
1	*Bacillus subtilis*	—	—	+ + +
2	*Pseudomonas aeruginosa*	— Pigment formation seen	— Pigment formation seen	+ + + No Pigment formation seen

+ + + indicate profused growth; -indicate no growth

The studies pertaining to antimicrobial activity showed that the sample inhibited *Bacillus subtilis* growth when compared to control at both concentrations.

Pseudomonas aeruginosa showed no growth but bluish green pigmentation was seen.



S.No	Ar	Molecular formula	M.P°C	Yield%
1	p-chloro phenyl	$C_{17}H_{13}ClN_4O_3$	180	68
2	p-methyl phenyl	$C_{18}H_{16}N_4O_3$	165	65
3	p-methoxy phenyl	$C_{18}H_{16}ClN_4O_4$	160	62
4	m-nitro phenyl	$C_{17}H_{13}N_5O_5$	140	67

Table of I.R Spectra

S.No	Ar	>C=O cm^{-1}	NH cm^{-1}
1	p-chloro phenyl	1595.8	3342
2	p-methyl phenyl	1716.4	3351
3	p-methoxy phenyl	1721	3351
4	m-nitro phenyl	1716	3224.8

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