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옥사졸론 유도체의 합성과 항균성

M. J. Aaglawe, S. S. Dhule, S. S. Bahekar, P. S. Wakte, and D. B. Shinde*
Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad- 431004 (M.S.) India
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Synthesis and Antibacterial Activity of Some Oxazolone Derivatives

M. J. Aaglawe, S. S. Dhule, S. S. Bahekar, P. S. Wakte, and D. B. Shinde*
Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad- 431004 (M.S.) India
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요 약. 일련의 옥사졸론 유도체들을 (**4a-n**) 항균제로서 합성하였다. 이 화합물들은 아릴옥시아세틸아미노아세트산을 에탄올, 아세트산 무수물, 아세트산 소듐 존재하에 알데하이드와 반응시켜 합성하였으며 핵자기공명 스펙트럼과 적외선 스펙트럼으로 구조를 확인하였다.

주제어: 치환된 4-옥사졸-5 유도체, 항균성 합성

ABSTRACT. A series of oxazolone derivatives (**4a-n**) have been synthesized as a potential antibacterial agent. Titled compounds have been prepared by the condensation of aryloxy acetyl-amino-acetic acid with aldehyde in presence of ethanol, acetic anhydride and sodium acetate. The structures of the new compounds were established on the basis of ^{1}H NMR and IR spectral data.

Keywords: Substituted 4-Oxazol-5-One's , Antibacterial Activity, Synthesis

INTRODUCTION

Heterocyclic compounds are acquiring more importance in recent years due to the pharmacological activities. Nitrogen, sulphur, oxygen containing five/six member heterocyclic compounds has occupied enormous significance in the field of medicinal chemistry. Oxazole plays very vital role in the manufacturing of various biologically active drug as analgesic,[1] anti-inflammatory[2], antidepressant,[3] anti-cancer,[4] anti-microbial, anti-diabetic and antiobesity.[5,6] In view of this, it was of considerable interest to synthesize the title compound with a hope to obtain potent biologically active compound.

CHEMISTRY

The synthetic routes are outlined in scheme1, the titled compound 4-substituted aryl 2-4-substituted phenloxy methyl 4-oxazol-5-one (**4a-n**) was synthesised by reacting aryloxy acetyl-amino-acetic acid with suitable aldehydes in presence of ethanol, acetic anhydride and sodium acetate. Literature survey reveals that less attention is given to the synthesis of oxazole nucleus having ether link agent at second position. Some workers[7,8] have reported the oxazole nucleus having phenyl, methyl and benzothiophene moietis at second position. The oxazole with ether linkage at fifth position are found to possess good anti-bacterial, anti-inflammatory and CNS

Table 1. Characterisation data of titled compounds (**4a-n**)

No.	R	R1	C % Calc. (Found)	H % Calc. (Found)	N % Calc. (Found)	MP °C	Mol. Formula Mol. Wt.	IR-(KBr) cm^{-1}	^1H NMR-($CDCl_3$)
4a	H	phenyl	73.11 (73.08)	4.69 (4.71)	5.02 (5.03)	105	$C_{17}H_{13}NO_3$ 279	1288(C-Ostretch), 1685(C=O), 3000 (C=CAromatic)	2.3(s, 3H, -CH_3), 4(s, 2H, O-CH_2-), 6.7-7.8 (m, 11H, Ar-H &=CH-)
4b	H	p-chlorophenyl	65.08 (65.07)	3.86 (3.87)	4.46 (4.47)	130	$C_{17}H_{12}ClNO_3$ 313	1270(C-Ostretch), 1680(C=O),3 000 (C=CAromatic)	2.3(s, 3H,-CH_3), 4.2(s, 2H, O-CH_2-), 6.6-7.9(m, 10H, Ar-H &=CH-)
4c	H	p-methoxy	69.89 (69.90)	4.89 (4.91)	4.53 (4.52)	135	$C_{18}H_{15}NO_4$ 309	1250(C-Ostretch), 1705(C=O), 2990 (C=CAromatic)	2.45(s, 3H, -CH_3), 3.75(s, 3H, O-CH_3 4.1(s, 2H, O-CH_2-), 6.4-7.8(m, 10H, Ar-H &=CH-)
4d	H	3-nicotin	68.56 (68.55)	4.32 (4.33)	9.99 (9.98)	132	$C_{16}H_{12}N_2O_3$ 280	1260(C-Ostretch), 1725(C=O), 3000 (C=CAromatic)	2.36(s, 3H, -CH_3), 4.1(s, 2H, O-CH_2-), 6.6-8.9(m, 10H, Ar-H &=CH-)
4e	H	2-thiophene	63.14 (63.13)	3.89 (3,92)	4.91 (4.93)	107	$C_{15}H_{11}NO_3S$ 285	1260(C-Ostretch), 1700(C=O), 3030 (C=CAromatic)	2.45(s, 3H, -CH_3), 3.97(s, 2H, O-CH_2-), 6.5-7.6(m, 9H, Ar-H &=CH-)
4f	H	furfural	66.91 (66.89)	4.12 (4.14)	5.20 (5.22)	145	$C_{15}H_{11}NO_4$ 269	1230(C-Ostretch), 1685(C=O), 2950 (C=C-HAromatic)	2.4(s, 3H,-CH_3), 4(s, 2H, O-CH_2-), 6.4-7.8(m, 9H, Ar-H &=CH-)
4g	H	m-bromophenyl	57.00 (57.01)	3.38 (3.39)	3.91 (3.92)	165	$C_{17}H_{12}BrNO_3$ 358	1250(C-Ostretch), 1685(C=O), 3000 (C=C-HAromatic)	2.49(s, 3H, -CH_3), 4.12(s, 2H, O-CH_2-), 6.6-7.6(m, 10H, Ar-H &=CH-)
4h	CH_3	phenyl	73.71 (73.70)	5.15 (5.17)	4.78 (4.76)	109	$C_{18}H_{15}NO_3$ 293	1270(C-Ostretch), 1735(C=O), 3000 (C=CAromatic)	2.35(s, 3H, -CH_3), 4(s, 2H, O-CH_2-), 6.4-7.8(m, 10H, Ar-H &=CH-)
4i	CH_3	p-chlorophenyl	65.96 (65.96)	4.31 (4.33)	4.27 (4.26)	126	$C_{18}H_{14}ClNO_3$ 327	1255(C-Ostretch), 1715(C=O), 3000 (C=C-HAromatic)	2.4(s, 3H, -CH_3), 4.0 (s, 2H, O-CH_2-), 6.5-7.8(m, 9H, Ar-H &=CH-)
4j	CH_3	p-methoxy	70.58 (70.56)	5.30 (5.31)	4.33 (4.32)	147	$C_{19}H_{17}NO_4$ 323	1250(C-Ostretch), 1685(C=O), 3000 (C=C-HAromatic)	2.35(s, 3H,-CH_3), 3.67(s, 3H, O-CH_3 4.1(s, 2H, O-CH_2-), 6.4-7.8(m, 9H, Ar-H &=CH-)
4k	CH_3	3-Nicotin	69.38 (69.36)	4.79 (4.80)	9.52 (9.50)	150	$C_{17}H_{14}N_2O_3$ 294	1245(C-Ostretch), 1685(C=O), 3000 (C=C-HAromatic)	2.3 (s, 3H, -CH_3), 4.2(s, 2H, O-CH_2-), 6.6-8.9(m, 9H, Ar-H &=CH-)
4l	CH_3	2-Thiophene	64.20 (64.22)	4.38 (4.36)	4.68 (4.69)	113	$C_{16}H_{13}NO_3S$ 299	1240(C-Ostretch), 1695(C=O), 3000 (C=C-HAromatic)	2.45(s, 3H, -CH_3), 4.1(s, 2H, O-CH_2-), 6.5-7.6(m, 8H, Ar-H &=CH-)
4m	CH_3	Furfural	67.84 (67.81)	4.63 (4.61)	4.94 (4.95)	135	$C_{16}H_{13}NO_4$ 283	1270(C-Ostretch), 1735(C=O), 3000 (C=CAromatic)	2.5(s, 3H, -CH_3), 4(s, 2H, O-CH_2-), 6.4-7.8(m, 8H, Ar-H &=CH-)
4n	CH_3	m-bromophenyl	58.08 (58.10)	3.79 (3.80)	3.76 (3.72)	172	$C_{18}H_{14}BrNO_3$ 372	1260(C-Ostretch), 1725(C=O), 3000 (C=CAromatic)	2.39(s, 3H, -CH_3), 4.2(s, 2H, O-CH_2-), 6.6-7.6(m, 9H, Ar-H &=CH-)

C,H,N,S.microanalysis (± 0.4 % of the calculated values) was obtained for all the compounds(**4a-n**).

activity.[9] The titled compound (**4a-n**) is having ether linkage at second position. The structures of the synthesized compounds have been determined by their elemental analysis, IR, ^{1}H NMR spectra and their physical properties are listed in the *Table* 1.

Pharmacological activity

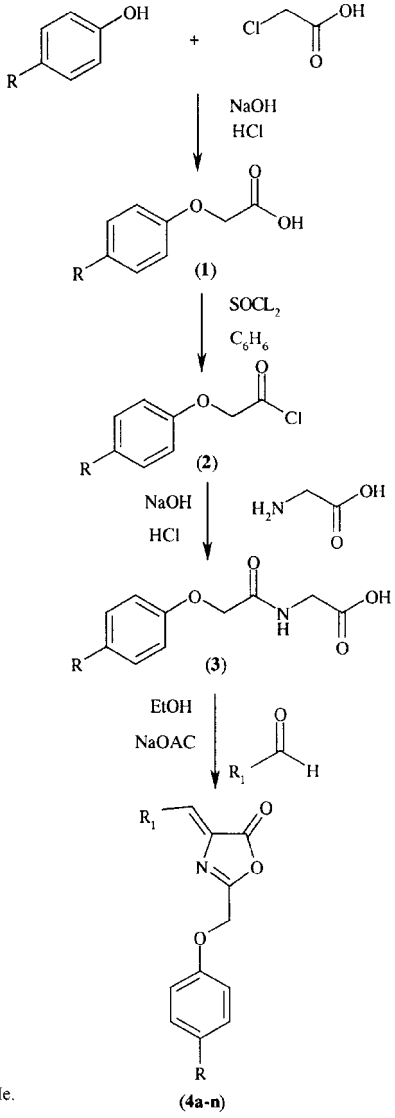
All the compounds (**4a-n**) were screened for their *in vitro* antibacterial activity against *E. coli* and *Xanthomonas citri* by cup-plate method[10] summarized in table II. Nutrient agar was melted in a water bath and cooled to 45 °C with gentle shaking to bring about uniform cooling. It was inoculated with 0.5-0.6 mL of culture and mixed well by gentle shaking before pouring onto the sterilized petri dishes. The poured materials were allowed to set and there after the "CUPS" were made by punching into the agar surface with sterile cork borer and scooping out the punched part of the agar. Into these cups were added 0.1 mL. portion of the test compound in the solvent with the help of sterile syringe. The drug solution was allowed to diffuse for about an hour into the medium. The plates were incubated at 37 °C and the results noted. From the activity data it was concluded that all the compounds (**4a-n**) shows antibacterial activity against *E. coli* and *Xanthomonas citri* as compared to reference standard Streptomycin. Amongst all compounds **4b**, **4i**, **4k** and **4n** shows highest antibacterial activity against *E. coli* and compounds **4a**, **4b**, **4h**, **4i** and **4l** shows highest activity against *Xanthomonas citri*.

EXPERIMENTAL

The melting points were taken in open capillary and are uncorrected. The purity of compounds was checked by TLC. IR spectra were recorded on JASCO spectrophotometer Japan using KBr pellets. ^{1}H NMR spectra in $CDCl_3$ on a sophisticated multinuclear FT-NMR spectrophotometer model Ac-300 F (Bruker Germany) 300 MHz using TMS as an internal standard. Satisfactory microanalysis (± 0.4% of the calculated values) was obtained for all the compounds.

Synthesis of Phenoxy -acetyl-amino acetic acid (3)

To a mixture of monochloroacetic acid (0.05 mol) phenol (0.05 mol), a solution of sodium hydroxide (0.12 mol in 25 mL water) was added slowly with constant stirring. After completion of addition, the mixture was stirred for 2hr till solution turn greenish yellow and then evaporated till sodium salt precipitates out. The salt was dissolves in water and acidified with conc. HCl till Congo red paper turn blue. The Phenoxy acetic acid (**1**) thus obtained was filtered off. Then Phenoxy acetic acid (0.01mol) **(1)** was converted in to acid chloride using thionyl chloride and benzene. After this the excess of thio-



Where
R=H, Me.
R_1=Aryl.

Scheme 1.

Table 2. Antibacterial activity Data of compounds (**4a-n**)

No.	*E. coli* (zone in mm)	*X. citri* (zone in mm)
4a	08	13
4b	12	15
4c	10	11
4d	08	10
4e	11	08
4f	09	10
4g	13	12
4h	10	13
4i	12	14
4j	09	09
4k	12	08
4l	07	13
4m	10	11
4n	11	10
Standard (Streptomycin)	12	14

nyl chloride was distilled out under reduced pressure, the resultant Phenoxy -acetyl chloride (**2**) in the form of viscous liquid was collected. The resulting Phenoxy -acetyl chloride (**2**) further added to a solution of glycine (0.01 mol) in NaOH (0.12 mol in 25 mL water) with continuous stirring, the product thus obtained was dissolved in water and acidified with HCl to get phenoxy acetyl amino-acetic acid (**3**).

Synthesis of 4-substituted aryl 2-4-substituted phenloxy methyl 4-oxazol-5-one (4a)

A mixture of Phenoxy acetyl amino-acetic acid (0.01 mol) (**3**), aldehyde (0.01 mol), acetic anhydride (5 mL) and sodium acetate (0.01 mol) was reflux for 4 hr. It was then cooled and ethanol (10 mL) was added it. The resulting mixture was left over night at room temp. The solid thus obtained was filtered, washed with cold ethanol, dried and crystallized from hexane to get title compound (**4a**).

All new titled compounds (**4a-n**) were synthesized by following the same procedure (see *Scheme* I). The characterisation data of titled compounds is summarized in *Table* 2.

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