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Synthesis and Antimicrobial Activity of Some Substituted Azetidine-2-Ones

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The titled derivatives have been synthesized by condensing aryl and aryloxy acetyl chloride in presence of triethyl amine (TEA) with 1N-amino benzal-2-phenyl-4-arylidene-Δ2-imidazolin-5-ones, obtained by the reaction of 1N-amino-2-phenyl-4-arylidene-Δ2-imidazolin-5-ones with different aromatic aldehydes. The products have been characterised by IR, NMR and elemental analysis and have been screened for their antimicrobial activity.

INTRODUCTION

A large number of antibiotics contain a β-lactam heterocyclic moiety[1]. β-Lactams are known to possess various biological activity[2]. Survey of literature reveals no support on the synthesis of 2-azetidinones bearing oxazolinone. Keeping this in view and in continuation of our heterocyclic synthesis[3], synthesis of some novel azetidine-2-one **IV**, were carried out by condensing aryl and aryloxy-acetyl chlorides in presence of triethylamine with 1N-aminobenzal-2-phenyl-4-arylidene-2-imidazolin-5-one, **II**. **II** was prepared by the reaction of hydrazine hydrate with 2-phenyl-4-arylidene-oxazoline-5-ones **I**. **I** was prepared as reported[4].

During synthesis of substituted azetidin-2-ones, we came across different synthetic routes adopted by different workers for the synthesis of substituted azetidine-2-one. Parekh[5] and Joshi[6] synthesized azetidines requiring 5 h stirring and keeping the reaction mixture for 3 days for the reaction of acetyl chloride/chloro acetyl chloride with Schiff bases, using dioxane as solvent and triethylamine (TEA) as a catalyst reporting 65% yield. Dave[7] has used dry benzene as solvent and TEA as a catalyst requiring 3 h stirring but low yield (48%). Kidwai et al.[8] used dichloromethane as solvent requiring 5 to 8 h, giving 61% yield. Bhat *et al.*[9] have reported in their synthesis of azetidinone using dry benzene as solvent, a few drops of TEA and refluxing the reaction mixure for 2 h, giving 68 to 75% yield.

We used all the above reported five methods for our synthesis of azetidin-2-one derivatives. We compared the reaction time, yield and purity of the product(s). It was inferred that Bhat[9] method with a little modification is quite workable in our case with good yield and requiring less time as compared to other methods. The isolation of the product was also easier.

The products have been characterised by IR, NMR and elemental analysis and have been screened for their antimicrobial activity.

The synthesized compounds were screened for antibacterial[10] activity at 100 μg concentrations against *E. coli, Klebsiella* and *Pseudonomonas*. Disc and plate dilution methods were used and penicillin was taken as a standard drug for

TABLE-1
PHYSICAL DATA OF COMPOUNDS

Compound	Substituents			Yield (%)	m.p (°C)	R_f	Analysis, % Calcd. (Found)		
	R	R′	R″				C	H	N
IV a	C_6H_5	C_6H_5	C_6H_5	85	210	0.70	79.65 (79.61)	4.90 (4.87)	8.99 (8.95)
IV b	C_6H_5	C_6H_4—OCH_3	C_6H_5	80	215	0.62	77.26 (77.22)	5.01 (5.00)	8.45 (8.41)
IV c	C_6H_4—OCH_3	C_6H_5	C_6H_5	81	216	0.68	77.26 (77.24)	5.01 (4.00)	8.45 (8.40)
IV d	C_6H_4—OCH_3	C_6H_4—OCH_3	C_6H_5	68	190	0.65	75.14 (75.12)	5.10 (5.08)	4.83 (4.80)
IV e	C_6H_4—NO_2	C_6H_5	C_6H_5	83	215	0.72	72.65 (72.63)	4.28 (4.25)	4.83 (4.80)
IV f	C_6H_4—NO_2	C_6H_4—OCH_3	C_6H_5	85	235	0.58	70.58 (70.52)	4.39 (4.35)	10.29 (10.25)
V a	C_6H_5	C_6H_5	H	63	212	0.63	76.53 (76.50)	4.83 (4.80)	10.71 (10.70)
V b	C_6H_5	C_6H_4—OCH_3	H	82	193	0.67	73.93 (73.91)	4.96 (4.92)	9.95 (9.90)
V c	C_6H_4—OCH_3	C_6H_5	H	75	218	0.60	73.93 (73.90)	4.96 (4.92)	9.95 (9.93)
V d	C_6H_4—OCH_3	C_6H_4—OCH_3	H	77	210	0.70	71.68 (71.65)	5.07 (5.04)	9.29 (9.25)
V e	C_6H_4—NO_2	C_6H_5	H	85	208	0.68	68.64 (68.60)	4.10 (4.08)	12.81 (12.80)
V f	C_6H_4—NO_2	C_6H_4—OCH_3	H	83	219	0.62	69.17 (69.15)	4.72 (4.70)	12.41 (12.40)

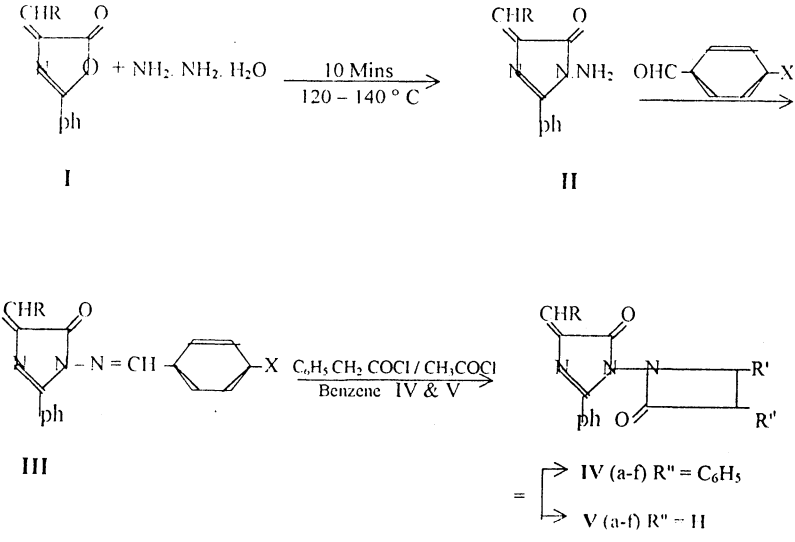
TABLE-2
DATA FOR ANTIMICROBIAL ACTIVITY (in mm)

Compound	*E. coli*	*Kleb-siella*	*Pseudo-monas*	Compound	*E. coli*	*Kleb-siella*	*Pseudo-monas*
IVa	9	5	—	**Va**	12	11	8
IVb	11	3	—	**Vb**	14	6	6
IVc	8	—	5	**Vc**	6	7	—
IVd	7	—	4	**Vd**	4	4	—
IVe	6	14	7	**Ve**	8	—	6
IVf	4	16	4	**Vf**	7	5	8
				Std. (Penicillin)	20	18	15

— No activity

comparison **IVa, Va, Vb** were prominent in activity against *E. coli.* **IVe, Vf** were prominent in activity against *Klebsiella*, comparable to penicillin. **IVa, IVc, IVe,** exhibited activity againt *E. coli* **Va, Vf** exhibited no activity against *klebsiella* whereas **IVa, IVb, Vc** and **Va** exhibited no activity against *Psuedonomonas.*

IR (cm^{-1}): 3404 ν(N—H), 2925 ν(CH_2), 2838 ν(OCH_3), 1736 ν(C=O of β-lactam), 1666 ν(C=N); **Vc**: ^1H NMR (DMSO-d^{6}): δ3.80 (s, $3H_1$—OCH_3), 5.0 (d, 1H, CH), 5.2 (t,1H, CH_2), 6.9 (d, 1H, CH_2) 6.98 (s, 1H,: CH), 7.4–7.8 (m, 14H, Ar—H)



EXPERIMENTAL

Melting points are uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer spectrometer and ^1H NMR spectra on a Brucker Ac 300F NMR spectrometer at 300 MHz. The purity of the compounds was checked by TLC using silica gel G.

1. *Synthesis of 1N-amino-2-phenyl-4-arylidene-Δ2-imidazoline-5-ones,* **II**: 2-Phenyl-4-arylidene-oxazolin-5-ones, **I** (prepared as per Vogel's method) (0.01 mol) and hydrazine hydrate (0.01 mol) were taken in a R.B. flask. The reaction mixure was heated in an oil bath at 120–140°C for 10 min. It was cooled white compound separated was filtered and crystallised from rectified spirit to get **II.**

2. *Synthesis of 1N-amino-benzal-2-phenyl-arylidene-2-imidazolin-5-one (Schiff base)* **III**: **III** was prepared by condensing **II** with different aromatic aldehydes in presence of a drop of conc. H_2SO_4. **II** (0.01 mol) was dissolved in rectified spirit (10 mL). A drop of conc. H_2SO_4 was added to it. The reaction

mixure was refluxed for 30 min on water bath. The solid separated was filtered hot and crystallised from rectified spirit.

Synthesis of Acid Chlorides

Aryl/aryloxy acetic acid (0.1 mol) was dissolved in dry benzene (10 mL). To this thionyl chloride (0.2 mol) was added dropwise with occasional stirring. The mixure was refluxed for 2 h. More benzene was added and excess of thionyl chloride was distilled off and the remaining solution of acid chloride in benzene directly used for the next step.

3. *Synthesis of 1 (2-phenyl-4-4arylidene-5-oxazoline-1-yl)3-phenyl-4-aryl-azetidin-2-one,* **IV**: To a solution of **III** (0.02 mol) in dry benzene (30 mL) were added a few drops of TEA. A solution of phenyl acetyl chloride (0.02 mol) in benzene was added with stirring and refluxed for 2 h. Triethyl amine hydrochloride formed was filtered off and washed 2–3 times with dry benzene. The filtrate and washings were concentrated under reduced pressure. The residue obtained was dried and crystallised from ethanol.

4. *Synthesis of 1 (2-phenyl-4-arylidene-5-oxazolino-1-yl)-4-aryl-azetidine-2-one,* **V**: To a solution of **III** (0.02 mol) in dry benzene (30 mL) was added a few drops of TEA. A solution of acetyl chloride (0.02 mol) in benzene were added with stirring and refluxed for 2 h. Triethyl amine hydrochloride formed was filtered off and washed 2–3 times with dry benzene. The filtrate and washings were concentrated under reduced pressure. The residue obtained was dried and crystallised from ethanol.

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