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Microwave Synthesis of Novel Imidazetines as Bilactam Antimicrobial Agents

NEELAVENI THANGAVEL*, SANKAR LAKSHMAN†, SUBHA BALAKRISHNAN†, RAMAN SARASWATHI and NEELAKANDAN KRISHNAN†

Department of Pharmaceutical Chemistry, PSG College of Pharmacy
Peelamedu, Coimbatore-641 004, India
E-mail: venivelu2004@yahoo.co.in

The condensation of various substituted phenyl urea and monocarboxylic acids were carried out by conventional method using hydrochloric acid (4 N). The amides and acids in ethanol were also condensed under microwave irradiation since the time utilized by the conventional method was so long, up to 10 h. The results indicate that microwave irradiation enhances the rate of reaction and the yield was also improved. Minimum inhibitory concentrations were determined by serial dilution method and the zones of inhibition against various pathogens were also determined using cup-plate method. The compounds synthesized exhibited varying degrees of antimicrobial activity and the lyses produced were comparable with the standard drugs.

Key Words: Microwave, Synthesis, Imidazetines, Bilactam antimicrobial agents.

INTRODUCTION

The role of medicinal compounds possessing —CON linkage is extensively known as sedatives, anticonvulsants, anti-psychotics, etc. Antibacterial agents like penicillin, cephalosporin, etc., are good examples of lactams[1]. Microwave enhanced organic reactions have been already used for the convenient synthesis of a number of heterocycles[2–6]. The present investigation is an effort to synthesize imidazetines as lactams and this is the first report on synthesis of imidazetines through condensation of substituted phenyl urea and monocarboxylic acids. The synthesis by conventional method required long reaction times affording lower yields, so microwave enhanced synthesis of imidazetines was carried out and the results are reported.

EXPERIMENTAL

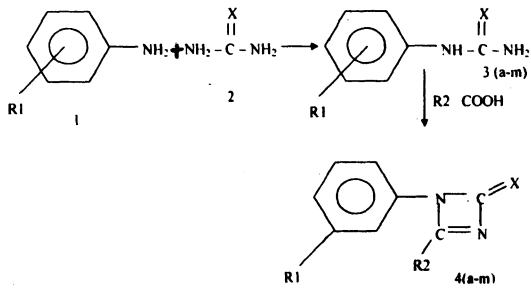
All melting points were determined in open capillary tubes and are uncorrected. IR spectra was recorded as KBr pellets (cm^{-1}) on Perkin-Elmer FTIR-1600 spectrophotometer, PMR on a Varian Perkin-Elmer R-32 (90 MHz) spectrometer using $CDCl_3$ as solvent and TMS as internal standard. TLC was run on silica gel G plates and spots were identified by iodine vapours.

Various substituted phenyl ureas **(3a–m)** were synthesized by condensing substuted phenyl ureas **(1)** with urea/thiourea **(2)** according to the reported method[7, 8].

†RVS College of Pharmaceutical Sciences, Sulur, Coimbatore-641 402, India.

General procedure for the synthesis of 3-aryl, 4-oxo/thio imidazetines

The substituted phenyl urea (0.025 mol) **(3a–m)** was dissolved in alcohol and 0.025 mol of organic acid (R_2COOH) was added and 2 mL of 4 N HCl was added and refluxed continuously for 5–10 h. The solution was then cooled overnight and the solid obtained was filtered and dried. The crude products **(4a–m)** were recrystallized from alcohol or chloroform and alcohol. **(Scheme-1).**



Scheme-1

Microwave enhanced synthesis: A mixture of equimolar quantities (mmol) of substituted phenyl urea **(3a–m)** and various organic acids were taken in ethanol (10 mL) in a 100 mL conical flask capped with a glass funnel and was irradiated in a domestic microwave oven of 100 W at power level 3 in a scale of 5 for 5 min. The reaction mixture was concentrated by rotary evaporator and the products were recrystallized with suitable solvents. The physical data are reported in Table-1.

TABLE-1
PHYSICAL DATA OF IMIDAZETINE BILACTAMS

Compounds	R_1	R_2	X	m.f. (m.p.) (°C)	Yield % (w/w)	N Calcd. (Found) %
4a	*m*-NO_2	—H	O	$C_8H_3N_3O_3$ (180)	92.5	21.98 (21.83)
4b	*o*-CH_3	—H	O	$C_9H_8N_2O$ (190)	88.5	17.50 (17.22)
4c	*m*-NO_2	—CH_3	O	$C_9H_7N_3O_3$ (150)	95.0	20.48 (20.26)
4d	*m*-NO_2	—C_6H_5	O	$C_{14}H_9N_3O_3$ (110)	90.5	15.73 (15.01)
4e	*m*-NO_2	—H	S	$C_8H_5N_3O_2S$ (212)	73.0	20.28 (20.42)
4f	*m*-NO_2	—CH_3	S	$C_9H_7N_3O_2S$ (222)	70.0	19.00 (19.05)
4g	*o*-CH_3	—H	S	$C_9H_8N_2S$ (204)	82.0	15.90 (15.65)
4h	*o*-CH_3	—C_6H_5	S	$C_{15}H_{12}N_2S$ (125)	91.8	11.11 (10.96)
4i	*p*-NO_2	—H	O	$C_8H_5N_3O_3$ (191)	93.6	21.98 (21.28)
4j	*p*-NO_2	—CH_3	O	$C_9H_7N_3O_3$ (186)	94.2	20.48 (19.98)
4k	*p*-NO_2	—C_6H_5	O	$C_{14}H_9N_3O_3$ (132)	92.6	15.73 (15.25)
4l	*p*-NO_2	—H	S	$C_8H_5N_3O_2S$ (202)	85.5	20.28 (20.00)
4m	*p*-NO_2	—CH_3	S	$C_9H_7N_3O_2S$ (206)	86.2	19.00 (18.85)

The compounds **(4a–m)** were screened for antimicrobial activity against pathogenic microorganisms like *Staphylococcus aureus, Escherichia coli, Pseudomonas aeuroginosa, Shigella* and *Candida albicans.* Minimum inhibitory concentrations were determined using serial dilution method. Zones of inhibition were also determined using cup-plate method[9] and are reported in Table-2.

TABLE-2
ANTIMICROBIAL ACTIVITY OF IMIDAZETINE BILACTAMS*

Compd.	*S. aureus*		*E. coli*		*Shigella*		*P. aeuroginosa*		*C. albicans*	
	20 μg	40 μg	20 μg	40 μg	20 μg	40 μg	20 μg	40 μg	20 μg	40 μg
4a	24.0±0.9	28.0±0.8	26.0±1.5	30.0±0.9	—	22.0±1.5	—	16.5±0.5	21.0±1.0	33.0±1.1
4b	19.9±0.8	26.0±0.8	20.0±1.5	28.0±1.5	—	20.0±1.2	—	16.8±0.5	20.1±0.8	26.0±1.5
4c	30.0±0.9	32.7±1.0	30.0±1.1	32.0±1.5	22.0±0.5	26.0±1.6	—	23.0±0.5	28.0±0.5	35.0±0.5
4d	30.0±0.8	32.0±0.8	30.0±0.1	32.0±0.6	—	20.0±1.9	—	25.0±1.2	28.0±0.6	34.0±1.1
4e	—	12.0±1.0	—	6.5.0±0.8	—	16.0±1.2	—	20.0±1.5	26.0±1.3	31.0±1.5
4f	17.5±0.6	22.0±1.5	20.0±0.5	24.0±0.8	—	20.5±0.3	—	15.2±0.5	22.0±0.6	32.0±1.5
4g	18.0±1.1	20.0±1.5	20.0±0.5	24.0±0.8	—	25.0±0.7	14.0±0.5	19.5±0.8	22.0±1.1	32.0±1.1
4h	12.0±0.7	18.1±0.3	21.0±1.5	26.0±1.0	10.0±1.2	20.0±1.2	—	15.0±1.0	20.0±1.5	32.0±1.5
4i	14.0±0.9	20.0±0.8	12.1±0.5	22.0±1.5	12.0±0.5	18.5±0.3	—	14.5±0.2	20.0±1.5	28.0±1.4
4j	16.1±0.5	21.0±0.5	14.0±1.1	20.0±1.2	18.0±0.5	24.0±1.3	8.0±1.5	15.0±1.2	21.3±0.3	26.5±0.4
4k	16.5±1.0	20.0±1.5	21.5±0.3	27.0±1.2	10.0±1.2	16.0±1.3	8.0±1.5	16.0±1.5	18.2±0.5	22.0±1.6
4l	16.5±0.6	21.8±0.2	22.0±0.3	28.0±1.5	12.5±0.6	18.5±0.3	—	15.6±0.8	18.0±0.8	22.0±1.1
4m	12.5±0.6	18.5±0.3	20.0±0.6	28.0±0.6	—	12.0±1.2	10.0±1.2	18.5±0.3	16.0±1.2	22.0±1.5
Cip	22.5±1.1	38.0±0.6	26.0±0.8	40.0±1.2	22.0±1.2	30.0±0.5	15.0±1.2	30.0±1.2	—	—
Strep	—	36.0±1.2	—	32.2±0.3	—	28.0±1.5	—	25.0±1.2	—	—
Kle	—	—	—	—	—	—	—	—	30±2.5	38.3±0.5

*Zone of inhibitions in mm ± SEM. Readings are average of three determinations
Cip—Ciprofloxacin, Strep—Streptomycin (10 mg), Kle—Ketoconazole.

RESULTS AND DISCUSSION

The title compounds were synthesized successfully by condensation between phenyl urea and monocarboxylic acids in presence of 4 N HCl. The reaction can also take place by microwave irradiation in alcohol medium. Microwave enhanced condensation has taken place at a faster rate with reduced reaction time of 5 min which was more prolonged for 5–10 h in conventional method. The percentage yield with conventional method ranges from 55–75% whereas the yield obtained with microwave enhanced reaction ranges from 70–95% w/w. Since, the microwave assisted organic reactions need less amount of solvent and reagents and proceed without any environmental hazards, the suggested synthesis of imidazetines under microwave irradiation has wide scope in future. The products were characterized using spectral data and are in accordance with the

structures. The compounds were pure without any side products as indicated by TLC. The spectral data are as follows:

4a: 3-(3-nitro phenyl)-4-oxo imidazetine. IR : 1330, 1500, 1620, 1730. PMR: δ 2.5, 7.3, 7.4 (doublet).

4b: 3-(2-methyl phenyl)-4-oxo imidazetine. IR : 1230, 1620, 1775. PMR: δ 2, 2.4, 3.55, and 7.0.

4c: 2-methyl 3-(3-nitrophenyl)-4-oxo imidazetine. IR : 860, 990, 1230, 1320, 1490, 1710, 1590. PMR: δ 2, 2.5, 3.3, 3.7, 3.9 and 7.3.

4d: 2-phenyl 3-(3-nitro phenyl)-4-oxo imidazetine. IR : 710, 770, 820, 860, 1330, 1660, 1710, 3100. PMR: δ 7.2 and 7.4.

4e: 3-(3-nitro phenyl)-4-thio imidazetine. IR : 730, 770, 1220, 1270, 1330, 1490,1590. PMR: δ 2.2, 2.6, 3, 3.3, and 7.0.

4f: 2-methyl 3-(3-nitro phenyl)-4-thio imidazetine. IR : 710, 1070, 1330, 1440, 1500, 1600. PMR: δ 2.5, 3.3, 3.9 and 7.3.

4g: 3-(2-methyl phenyl)-4-thio imidazetine. IR : 735, 1230, 1330, 1430, 1590, 1630. PMR: δ 2, 2.4, 3.55, and 7.0.

4h: 2-phenyl 3-(2-methyl phenyl)-4-thio imidazetine. IR : 735, 1230, 1430, 1630 PMR: δ 2.4, 3.3 and 7.4.

4i: 3-(4-nitro phenyl)-4-oxo imidazetine. IR : 730, 1330, 1710. PMR: δ 2.5 and 7.58.

4j: 2-methyl 3-(4-nitro phenyl)-4-oxo imidazetine. IR (: 860, 1230, 1320, 1490, 1710. PMR: δ 2.5, 3.3, 3.7, 3.9 and 7.6.

4k: 2-phenyl-3 (4-nitro phenyl)-4-oxo imidazetine. IR : 770, 860, 1330, 1660, 1710, 3100. PMR: δ 7.2 and 7.6.

4l: 3-(4-nitro phenyl)-4-thio imidazetine. IR : 770, 1270, 1330, 1590. PMR: δ 2.2, 2.6, 3.0 and 7.6.

4m: 2-methyl-3-(4-nitro phenyl)-4-thio imidazetine. IR : 740, 1070, 1330, 1450, 1600, 1640. PMR: δ 2.5, 3.3, 3.9 and 7.5.

The IR data is discussed for **4a** as a representative case for oxo imidazetines and it gave a peak from 1730–1710 cm^{-1} for β-lactams, for thioimidazetines compounds show peaks at 1230 cm^{-1} and 1330 cm^{-1}. The PMR is discussed for **4c** as a representative case. The compounds show chemical shift at 2 for CH_3, 2.2, 2.6 for aromatic protons, splitting pattern at 3–3.55 for diortho aromatic protons. The other peaks are with respect to the structures. The minimum inhibitory concentrations in mcg/mL common to all the pathogens are as follows: **4a:** 10, **4b:** 10, **4c:** 5, **4d:** 5, **4e:** 15, **4f:** 15, **4g:** 12.5, **4h:** 20, **4i:** 20, **4j:** 10, **4k:** 10, **4l:** 10 and **4m:** 12. All the compounds exhibited moderate to good antimicrobial activity. Compounds **4c** and **4d** have a broad spectrum of activity and are more active than the other compounds. The activity may be due to the presence of CH_3 and C_6H_5 substituents on the second position of lactam ring and the 3-nitro group on the phenyl ring and the lactam ring itself.

It is concluded that an efficient, ecofriendly, high yield protocol for the synthesis of novel imidazetines has been developed and further studies are warranted for the antimicrobial property.

REFERENCE

1. J.N. Delgado, W.A. Remers, Wilson and Giswold, Text Book of Organic Medicinal and Pharmaceutical Chemistry, Lippincott-Raven Publishers, New York, p. 266 (1998).
2. R.A. Abramovitch and A. Bulman, *Synthlet.*, 795 (1998).
3. B.K. Banik, M.S. Manhas, Z. Kaluza, K.J. Baraka and A.K. Bose, *Tetrahedron Lett.*, **33**, 3603 (1992).
4. P. Ertl, M. Puciova and S. Toma, *Coll. Czech. Chem. Commun.*, **59**, 175 (1994).
5. I.C. Cotterill, A.Y. Usyatinsky, J.M. Arnold, D.S. Clark, J.S. Dordick, P.C. Michels and Y.L. Khmelnitsky, *Tetrahedron Lett.*, **39**, 117 (1998).
6. T. Besson and C.W. Rees, *J. Chem. Soc. Perkin Trans.*, *1*, 2857 (1996).
7. B.S. Furniss, A.J. Hannaford, P.W.G. Smith and A.R. Tatchill, in (Eds.): A.I. Vogel's Text Book of Practical Organic Chemistry, ELBS-Longmann, U.K., p. 965 (1995).
8. Susan Budavari, The Merck Index, Merck and Co., Inc., USA, pp. 75, 1476, 1502, 1553 (2002).
9. F. Kavanagah, Analytical Microbiology, Part II, Academic Press, New York, p. 126 (1972).

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