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ChemTech

International Journal of ChemTech Research
CODEN (USA): IJCRGG ISSN : 0974-4290
Vol.6, No.7, pp 3535-3539, Sept-Oct 2014

Synthesis and Antimicrobial Activity of Some Novel Ketimines

Borgaonkar V.V.[1]*, Patil B.R.[2]

[1]Department of Chemistry, Dnyanopasak College Parbhani-431401, MS, India.
[2]Department of Chemistry, Sharda Mahavidyalaya, Parbhani-431401, MS, India.

Corres.author: *vikas.borgaonkar@rediffmail.com*, *drbrp912@rediffmail.com

Abstract: As imines occupy central place among medicinally important compounds, novel bioactive iodo substituted ketimines were synthesized by the condensation of iodo substituted hydroxy aromatic ketones and aliphatic/aromatic amines using solvent free microwave irradiation method. This method provides advantages such as environmental friendliness, short reaction time with excellent yield. All the synthesized products were screened for their antimicrobial activity. The results indicated that some synthesized compounds show good antibacterial as well as antifungal activities
Keywords:- Substituted hydroxypropiophenones, Ketimines, Microwave irradiation method, Antimicrobial activity

Introduction:-

The chemistry of the carbon-nitrogen double bond plays a significant role in the progress of chemical science. Ketimines are compounds carrying R-C=N-R_1 linkage. The imine group present in organic compounds is crucial to their biological behavior[1,2]. The biological activities of imines have fascinated to organic and medicinal researchers for many years. Recent studies on biological evaluation of imines revealed some to be antimalerial[3], anticancer[4], antimicrobial[5], anti-HIV[6], nematicidal[7], antifungal[8], antituberculosis[9], antidepressant and anti-inflammatory[10]. Imines are also regarded as privileged intermediates in the synthetic design of heterocyclic compounds such as thiazolidinone, azetidinone etc.[11]

The different iodoaromatic compounds have been the subject of numerous studies due to the importance in pharmacology and biochemistry[12]. They are used in the synthesis of many interesting natural products[13]. Iodoaromatic compounds were used in medicine as drug or diagnostic aids, contractors[14]. They have importance in medicinal and pharmaceutical research[15].

Microwave-assisted synthesis of imines remarkably decreases the time necessary to carry out reaction. Thus, microwave-mediated organic reactions take place more rapidly, safely, with high yields and making industrially important organic synthesis more eco-friendly[16,17].

From above review, imines of iodo compounds expected to broaden biological activity profile. The present piece of work has been undertaken to study the synthesis and antimicrobial profile of iodo substituted ketimines.

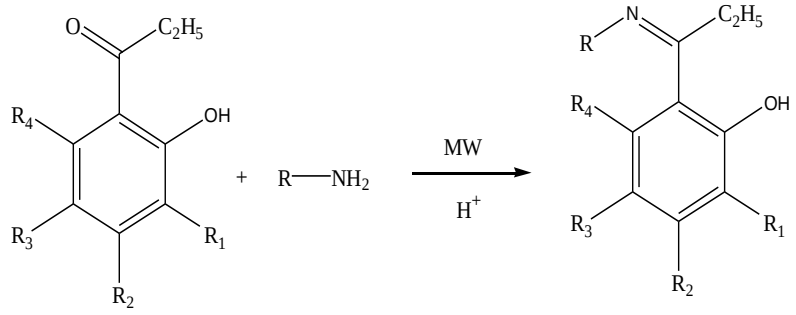
Materials and Methods:-

Melting points were determined in an open capillary tube and are uncorrected. IR spectra were recorded in KBr on a FTIR perkin-Elmer spectrometer. ^{1}HNMR spectra were recorded on Avance 300 MHz

spectrometer in $CDCl_3$ solvent. Mass spectra were taken on shimadzu QP2010 plus GC-MS. The iodo substituted aromatic ketones were prepared by literature method[18].

General Procedure:-

A mixture of iodo substituted 2- hydroxy propiophenones (0.01 mole) and aliphatic / aromatic amine (0.01 mole) along with 3-4 drops of glacial acetic acid was irradiated for appropriate time (Table 1) in Q-pro M modified microwave system at power level 500W. The progress of the reaction was monitored by TLC. After completion of reaction it was cooled and 25 ml icecold water was added. The reaction mixture was extracted with ethyl acetate (3 x 10 ml), organic layer was separated, dried over anhydrous sodium sulfate and evapourated to dryness. The crude product was recrystalized by ethanol to obtain pure crystals of desired compound 3(a-j).



1 **2** **3a-j**

Scheme I :- Synthesis of ketimines

Table – 1 : Physical and Analytical data of Ketimines

Entry	R_1	R_2	R_3	R_4	R	M.P. ^0C	Yield (%)	Time (Sec)	Elemental analysis (%) calculated (found)				
									C	H	N	Cl	I
3a	I	H	CH_3	H	*n*-C_3H_7	90	85	60	47.14 (47.79)	5.48 (5.03)	4.23 (4.65)	-	38.32 (38.03)
3b	I	H	CH_3	H	*n*-C_4H_9	97	90	60	48.71 (48.11)	5.84 (5.23)	4.06 (4.61)	-	36.76 (36.04)
3c	I	H	Cl	H	*n*-C_3H_7	84	83	60	40.99 (40.65)	4.30 (4.69)	3.98 (3.55)	10.08 (10.49)	36.09 (36.81)
3d	I	H	Cl	H	*n*-C_4H_9	87	88	60	42.70 (42.22)	4.69 (4.18)	3.83 (3.37)	9.70 (9.89)	34.71 (34.91)
3e	I	H	Cl	H	*iso*-C_3H_7	110	85	60	40.99 (40.62)	4.30 (4.95)	3.98 (3.20)	10.08 (10.59)	36.09 (36.90)
3f	I	H	Cl	H	C_6H_5	128	76	300	46.72 (46.31)	3.40 (3.03)	3.63 (3.99)	9.19 (9.89)	32.91 (32.19)
3g	Cl	H	I	H	C_6H_5	115	78	300	46.72 (46.31)	3.40 (3.03)	3.63 (3.99)	9.19 (9.89)	32.91 (32.19)
3h	CH_3	H	I	H	C_6H_4-CH_3	120	78	240	53.84 (53.16)	4.78 (4.12)	3.69 (3.97)	-	33.46 (33.79)
3i	CH_3	H	I	H	C_6H_4-OCH_3	135	81	180	51.66 (51.33)	4.59 (4.21)	3.54 (3.98)	-	32.11 (32.55)
3j	I	H	CH_3	H	CH_2-C_6H_5	130	78	240	53.84 (53.97)	4.78 (4.22)	3.69 (3.12)	-	33.46 (33.88)

3a) 2-iodo-4-methyl-6-[1-(propylimino) propyl] phenol:- Yellow Solid,

IR(KBr) : 3400(OH), 1610(C=N), 1533(>C=C<) cm^{-1}.**^{1}HNMR ($CDCl_3$)** :- δ 1.09 (t, 3H, H-3"), 1.90 (m, 2H,H-2"), 3.6(t, 2H, H-1"), 3.0(q, 2H, H-1'), 1.23 (t,3H, H-2'), 2.35 (s, 3H Ar-CH_3), 7.25- 7.80 (m,2H Ar-H), 13.10(s, 1H, -OH) ppm. **Mass:**-m/z – 331 $M^{+\cdot}$

3b) 2-(1-Butylimino-propyl)-6-iodo-4-methyl phenol:- Pale Yellow Solid,

IR(KBr) : 3480(OH), 1610(C=N), 1533(>C=C<) cm^{-1}. **^{1}HNMR ($CDCl_3$)** :- δ 0.93 (t, 3H, H-4"), 1.35 (m, 2H, H-3"), 1.66(m, 2H, H-2"), 3.62(t, 2H, H-1"), 2.9 (q, 2H, H-1'), 1.24 (t, 3H, H-2'), 2.35 (s, 3H,Ar- CH_3), 7.20 - 7.35 (m, 2H, Ar- H), 16.05 (s, 1H, -OH) ppm.

Mass:-m/z – 345 $M^{+\cdot}$

3c) 4-Chloro-2-iodo-6-(1-propylimino-propyl)-phenol:- Yellow Solid,

IR(KBr) : 3445(OH), 1610(C=N), 1534(>C=C<) cm^{-1}. **^{1}HNMR ($CDCl_3$)** :- 1.1 (t, 3H, H-3"), 1.9 (m, 2H, H-2"), 3.5 (t, 2H, H-1"), 2.8 (q, 2H, H-1'), 1.24 (t, 3H, H-2'), 7.85 - 8.07 (m, 2H, Ar- H), 16.05 (s, 1H, -OH) ppm. **Mass:-**m/z – 351 $M^{+\cdot}$

3d) 2-(1-Butylimino-propyl)-4-chloro-6-iodo-phenol:- Pale Yellow Solid,

IR(KBr) : 3442(OH), 1620(C=N), 1591(>C=C<) cm^{-1}. **^{1}HNMR ($CDCl_3$)** :- δ 1.09 (t, 3H, H-4"), 1.8 (m, 2H, H-3"), 2.4 (m, 2H, H-2"), 3.5 (t, 2H, H-1'), 2.86 (q, 2H, H-1'), 1.24 (t, 3H, H-2'), 7.83 -8.03 (m, 2H, Ar- H), 16.08 (s, 1H, -OH) ppm. **Mass:-**m/z – 365 $M^{+\cdot}$

3e) 4-Chloro-2-iodo-6-(1-isopropylimino-propyl)-phenol:- Yellow Solid,

IR(KBr) : 3449(OH), 1604(C=N), 1572(>C=C<) cm^{-1}. **^{1}HNMR ($CDCl_3$)**:- δ 1.20 (d, 6H), 3.40 (m, 1H), 2.9 (q, 2H, H-1'), 1.21 (t, 3H, H-2'), 7.9 - 8.01 (m, 2H, Ar- H), 16.10 (s, 1H, -OH) ppm. **Mass:-**m/z – 351 $M^{+\cdot}$

3f) 4-Chloro-2-iodo-6-(1-phenylimino-propyl)-phenol:- Bright yellow Solid,

IR(KBr) : 3442(OH), 1615(C=N), 1591(>C=C<) cm^{-1}. **^{1}HNMR ($CDCl_3$)**:- δ 1.22 (t, 3H, H-2'), 3.00 (q, 2H, H-1'), 7.06-7.80 (m, 7H), 14.75 (s, 1H, -OH) ppm. **Mass:-**m/z – 385 $M^{+\cdot}$

3g) 2-Chloro-4-iodo-6-(1-phenylimino-propyl)-phenol:- Bright Yellow Solid,

IR(KBr) : 3490(OH), 1631(C=N), 1575(>C=C<) cm^{-1}. **^{1}HNMR ($CDCl_3$)**:- δ 1.22 (t, 3H, H-2'), 3.00 (q, 2H, H-1'), 7.06-8.07 (m, 7H), 16.00 (s, 1H, -OH), ppm. **Mass:-**m/z – 385 $M^{+\cdot}$

3h) 4-Iodo-2-methyl-6-(1-p-tolylimino-propyl)-phenol:- Bright Yellow Solid,

IR(KBr) : 3430(OH), 1625(C=N), 1585(>C=C<) cm^{-1} . **^{1}HNMR ($CDCl_3$)**:- δ 1.21 (t, 3H, H-2'), 3.05 (q, 2H, H-1'), 2.90 (s, 3H, Ar- CH_3), 6.7-7.30 (m, 6H), 15.20 (s, 1H, -OH) ppm.

Mass:-m/z – 379 $M^{+\cdot}$

3i) 4-Iodo-2-[1-(4-methoxy-phenylimino)-propyl]-6-methyl-phenol:- Yellow Solid, **IR(KBr)** : 3480(OH), 1618(C=N), 1550(>C=C<) cm^{-1}. **^{1}HNMR ($CDCl_3$)**:- δ 1.24 (t, 3H, H-2'), 2.81 (q, 2H, H-1'), 2.85 (s, 3H, Ar-CH_3), 3.73 (s, 3H, -OCH_3), 6.64-7.25 (m, 6H), 16.10 (s, 1H, -OH) ppm. **Mass:-**m/z – 395 $M^{+\cdot}$

3j) 2-(1-Benzylimino-propyl)-6-iodo-4-methyl-phenol:- Pale yellow Solid,

IR(KBr) : 3443(OH), 1625(C=N), 1582(>C=C<) cm^{-1}. **^{1}HNMR ($CDCl_3$)**:- δ 1.21 (t, 3H, H-2'), 3.00 (q, 2H, H-1'), 2.35 (s, 3H, Ar-CH_3), 4.75 (s, 2H), 7.06-7.30 (m, 7H), 16.00 (s, 1H, -OH) ppm. **Mass:-**m/z – 379 $M^{+\cdot}$

Biological Activity:-

The Agar Cup Method is used to evaluate the antibacterial activity. Gram positive bacteria were grown in nutrient broth and gram negative bacteria in peptone water (Pw=1% bacteriological peptone and 0.5 % NaCl) for 18 hrs. Each purified compound was dissolved in DMSO to get desired concentration, the desired concentration of compound (100µl) was added in well of petri plate, Incubated at 37ºC up to 18 hrs for determination of the zone of inhibition. The diameters of the zones of complete inhibition were measured. The antifungal activity was evaluated by poison plate method. Potato dextrose agar was used as culture and DMSO was used to dissolve the compoumds (Dose 1%). It was observed that all compounds showed good antibacterial as well as antifungal activities. Results of both antibacterial and antifungal activities are shown in Table-2.

Table 2 : Antimicrobial activity of ketimines

Sr. No	Comp	Antibacterial activity Zone of Inhibition (mm)				Antifungal activity			
		S. aureus	B. subtilis	E. coli	P. auregenosa	A. niger	P. chrysogenum	F. moneliforme	A. flavus
1	3a	00	16	08	08	RG	+ve	+ve	+ve
2	3b	08	14	04	02	RG	RG	+ve	+ve
3	3c	04	24	08	02	-ve	RG	RG	+ve
4	3d	16	22	16	00	+ve	RG	RG	+ve
5	3e	12	22	16	04	-ve	RG	RG	+ve
6	3f	04	30	32	04	RG	RG	+ve	+ve
7	3g	00	18	14	00	RG	RG	+ve	+ve
8	3h	12	16	14	02	+ve	RG	RG	+ve
9	3i	08	16	08	00	+ve	RG	RG	+ve
10	3j	04	14	04	08	RG	RG	+ve	+ve
11	Std.	Vancomycine	Vancomycine	Vancomycine	Vancomycine	Griseofulvin	Griseofulvin	Griseofulvin	Griseofulvin
		18	30	30	18	-ve	-ve	-ve	-ve

+ve – Growth (Antifungal activity absent)
-ve – No Growth (Antifungal activity present
RG – Reduced Growth (More than 50% reduction in growth)

Results and Discussion:-

The novel ketimines were synthesized by solvent free microwave irradiation method. All the synthesized compounds were characterized by IR, ^{1}HNMR, Mass data. Synthesized compounds were consistent with their chemical structures. The characteristic IR band positions provided significant sign for the formation of the ketimines. The reaction was followed by disappearance of NH_2 absorption band at 3200-3346 cm^{-1} and appearance of band at 1600-1631 cm^{-1} for >C=N stretch vibrations which confirms condensation of carbonyl with amino group. Absorption at near 1479-1592 cm^{-1} is due to >C=C< aromatic stretch, absorption at 3400-3490 cm^{-1} is due to (2-OH) hydroxyl group. In addition confirmation for the formation of ketimines was obtained from the ^{1}H NMR spectra, which provide indicative tools for the positional clarification of the protons. Signal at δ 1.20-1.25 for -CH_2-$\underline{CH_3}$ and quartet at δ 2.80-3.05 for -$\underline{CH_2}$-CH_3 is observed in all compounds. The appearance of multiplets at δ 6.50–8.10 was due to aromatic protons. Common signal appearing at δ 13.00-16.23 is due to 2-OH group in all the compounds. The mass spectra of the synthesized compounds show the molecular ion peak confirming the molecular weight of the compounds.

Biological Activity- The data reported in Table 2 revealed that synthesized compounds tested for their antibacterial as well as antifungal activity. It was observed that compound 3f indicated extremely significant antibacterial activity against *B. subtilis* and *E. coli* compared to control. Some compounds indicated significant antibacterial activity against *B. subtilis, S. Aureus* and *E. coli* compared to control. Compounds 3c and 3e indicated good antifungal activity.

Conclusions:-

Novel ketimines were synthesized using microwave assisted solvent free conditions which provides advantages such as shorter reaction time, solvent free conditions, enhanced yields of products and eco friendly one. All synthesized compounds were screened for antibacterial activity against *S. Aureus, B. subtilis, E. coli and P. auregenosa* as well as Antifungal activity against *A.niger, P. chrysogenum, F. moneliforme, A. flavus.* It is observed that compound 3f is most active against *E.Coli,* and *B. subtilis,* compare to control. Many compoundes presents good activity against *S. Aureus, B. subtilis* and *E. coli,* while synthesized compoundes indicated moderate to poor activity against *P. auregenosa.* Compounds 3c and 3e indicated significant antifungal activity against *A.niger.* Some synthesized compounds acquire good antifungal activity against *A.niger, P. chrysogenum, F. moneliforme,* while synthesized compounds show poor activity against *A. flavus.* The results signified ketimines are capable of inhibiting the growth of bacteria and fungi to a good to moderate extent.

Acknowledgments

The authors are thankful to The Principal, Dnyanopasak College, Parbhani , The Principal, Sharda Mahavidyalaya, Parbhani and Dr. W. N. Jadhav, HOD, Dept. of chemistry, Dnyanopasak College, Parbhani for providing laboratory facilities. The authors are also thankful to IICT, Hyderabad for providing spectral data of synthesized compounds.

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