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Microwave induced solvent free synthesis of some novel bioactive bis-ketimines

Vikas V. Borgaonkar[1] and Bhagwan R. Patil*

[1]Organic Synthesis Research Laboratory, D. S. M. College Parbhani, MS, India
[*]Department of Chemistry, Sharda Mahavidyalaya, Parbhani, MS, India

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ABSTRACT

A series of novel bis-ketimines were synthesized by the reaction of substituted hydroxypropiophenones and ethylene diamine by classical and solvent free microwave irradiation method. All the synthesized compounds were characterized by IR, ^{1}HNMR, Mass data. The spectral data confirmed the structures of the synthesized compounds. All the synthesized products are screened for their in vitro antibacterial activity. The results signified that synthesized compounds have moderate to potent activities with respect to their appropriate reference standards and emerges as a potent antibacterial agents.

Keywords: Substituted hydroxypropiophenones, Bis-Ketimines, Microwave irradiation method, Ethylene diamine, Antibacterial activity.

INTRODUCTION

Utility of imines lay in their potent chemical and biological activity [1,2]. They have many comprehensive applications in medicinal, cosmetics, agriculture field. Their use in the field of inorganic and analytical chemistry is also worthy of note [3-5]. Pharmacologically important properties of Schiff bases like anticonvulsant, anti-inflammatory [6] were popularly studied. Imines have been reported as antibacterial [7], anticancer [8,9], anti-hypertensive and hypnotic [10], antifungal [11,12], antimicrobial [13], anti-tuberculosis [14,15], antifeedant [16] makes them attractive targets for medicinal synthetic chemists. Interesting role of imines is an intermediate in the biologically important transamination reaction [17]. Imines are versatile building blocks for the synthesis of new heterocyclic compounds incorporating thiazolidinone, azetidinone etc. [18,19]. This indicates imines as one of the biologically important scaffolds [20].

Owing to these facts large number of imines have been widely investigated from the aldehydic carbonyl source however significant attention have not given when precursors are ketocarbonyls since the synthesis of imines from aromatic ketones is far more difficult to achieve than from aldehydes [21] because of imine - enamine isomerisation.

Microwave technologies offer several advantages. Certain organic transformations which require several hours or even days to complete are effectively completed in minutes. Microwave assisted solvent free conditions provide advantages such as shorter reaction time, enhanced yields of products and eco friendly one [22,23].

In focus of these observations we report herein synthesis of ketimines from substituted hydroxypropiophenones with ethylene diamine by classical method and solvent free microwave irradiation method as an eco-friendly synthetic route, and investigated their antibacterial activities.

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 reported by our research group [24].

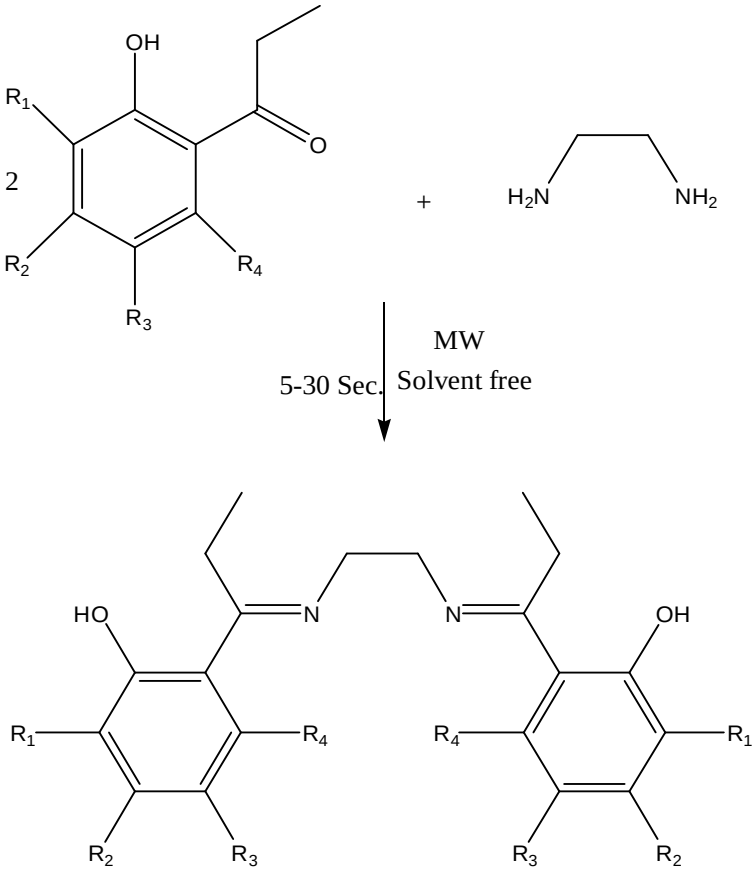
General procedure for synthesis of bis-ketimines :-

Method A

A mixture of substituted 2-hydroxypropiophenone (0.02mole) and ethylene diamine (0.01 mole) was refluxed in ethanol solvent for appropriate time (Table 1). The progress of the reaction was monitored by TLC. After completion of reaction as indicated by TLC, the reaction mixture was cooled, 25 ml ice cold water was added and the reaction mixture was extracted with ethyl acetate (3x10 ml). Organic layer was separated and dried over anhydrous sodium sulfate. Solvent was removed under vacuum to obtain crude product. The crude product was recrystalized by ethanol to obtain pure crystals of desired compound 3(a-k).

Method B

A mixture of substituted 2-hydroxypropiophenone (0.02mole) and ethylene diamine (0.01 mole) was irradiated for appropriate time (Table 1) in Q-pro M modified microwave system at power level 500W. After completion of reaction indicated by TLC, the reaction mixture was cooled, 25 ml ice cold water was added, and the reaction mixture was extracted with ethyl acetate (3x10 ml). Organic layer was separated and dried over anhydrous sodium sulfate. Solvent was removed under vacuum to obtain crude product. The crude product was recrystalized by ethanol to obtain pure crystals of desired compound 3(a-k).



3a-k

Scheme -1:- Synthesis of some novel bis-ketimines

Bis(α-ethyl-2-hydroxy)benzylidene-1,2-ethylene diamine (3a) :-

IR (KBr) : 3145(OH), 1625(C=N), 1555(C=C) cm^{-1} ; **^{1}HNMR ($CDCl_3$)** :- δ 1.23 (t, 6H), 2.80 (q, 4H), 4.00(s, 4H,2 x CH_2), 6.70-7.30(m,8H), 16.00 (s,2H, -OH) ppm; **M.S.-** *m/z* -324 $M^{+.}$

Bis(α-ethyl-2-hydroxy-5-chloro)benzylidene-1,2-ethylenediamine (3b) :-
IR (KBr) : 3180(OH), 1620(C=N), 1550(C=C) cm^{-1}; **^{1}HNMR ($CDCl_3$)** :- δ 1.20 (t,6H), 2.90 (q, 4H),4.00(s, 4H, 2 x CH_2), 6.79-7.80 (m,6H), 16.10(s, 2H,-OH) ppm; **M.S.-** *m/z* - 393 $M^{+\cdot}$

Table – 1 : Physical and Analytical data of Bis-ketimines

Entry	R_1	R_2	R_3	R_4	Mol. Formula	M.P.^{0}C	Yield(%)		Time(Sec)		Elemental analysis (%) calculated (found)				
							A	B	A	B	C	H	N	Cl	I
3a	H	H	H	H	$C_{20}H_{24}N_2O_2$	133	70	85	2400	30	74.04 (74.58)	7.46 (7.90)	8.64 (8.03)	-	-
3b	H	H	Cl	H	$C_{20}H_{22}Cl_2N_2O_2$	160	75	90	2100	25	61.08 (61.21)	5.64 (5.84)	7.12 (7.02)	18.03 (17.59)	-
3c	H	H	CH_3	H	$C_{22}H_{28}N_2O_2$	158	75	91	1500	15	74.97 (74.87)	8.01 (8.11)	7.95 (7.74)	-	-
3d	Cl	H	H	H	$C_{20}H_{22}Cl_2N_2O_2$	165	70	88	2100	30	61.08 (61.28)	5.64 (5.78)	7.12 (7.26)	18.03 (17.40)	-
3e	CH_3	H	H	H	$C_{22}H_{28}N_2O_2$	181	71	89	1200	5	74.97 (74.15)	8.01 (8.80)	7.95 (7.20)	-	-
3f	H	CH_3	H	H	$C_{22}H_{28}N_2O_2$	163	75	85	1800	25	74.97 (74.11)	8.01 (8.71)	7.95 (7.23)	-	-
3g	I	CH_3	I	H	$C_{22}H_{24}I_4N_2O_2$	178	70	85	2100	25	30.87 (30.05)	2.83 (2.15)	3.27 (3.77)	-	59.30 (59.89)
3h	I	H	Cl	H	$C_{20}H_{20}Cl_2I_2N_2O_2$	186	73	90	1500	10	37.24 (37.02)	3.12 (3.31)	4.34 (4.72)	10.99 (11.26)	39.34 (39.20)
3i	I	H	CH_3	H	$C_{22}H_{26}I_2N_2O_2$	200	75	91	1500	10	43.23 (43.50)	4.34 (4.21)	4.64 (4.80)	-	42.00 (42.31)
3j	Cl	H	I	H	$C_{20}H_{20}Cl_2I_2N_2O_2$	190	68	83	1800	20	37.24 (37.95)	3.12 (3.85)	4.34 (4.05)	10.99 (10.20)	39.34 (39.11)
3k	CH_3	H	I	H	$C_{22}H_{26}I_2N_2O_2$	195	68	85	1800	20	43.23 (43.07)	4.34 (4.04)	4.64 (4.98)	-	42.00 (42.85)

Bis(α-ethyl-2-hydroxy-5-methyl)benzylidene-1,2-ethylene diamine (3c) :-
IR (KBr) : 3190(OH), 1629(C=N), 1592(C=C) cm^{-1}; **^{1}HNMR ($CDCl_3$)** :- δ 1.23 (t,6H), 2.80 (q,4H), 3.90(s, 4H,2 x CH_2),2.30 (s, 6H, Ar-CH_3), 6.79-7.60 (m, 6H), 16.05(s, 2H, -OH) ppm; **M.S. -** *m/z* -352 $M^{+\cdot}$

Bis(α-ethyl-2-hydroxy-3-chloro)benzylidene-1,2-ethylene diamine (3d) :-
IR (KBr) : 3140(OH), 1618(C=N), 1567(C=C) cm^{-1};**^{1}HNMR ($CDCl_3$)** :- δ 1.24 (t,6H), 2.85 (q,4H), 3.91(s, 4H, 2 x CH_2), 6.50- 7.80 (m, 6H), 16.15(s, 2H, -OH) ppm; **M.S.-** *m/z*- 393 $M^{+\cdot}$

Bis(α-ethyl-2-hydroxy-3-methyl)benzylidene-1,2-ethylene diamine (3e) :-
IR (KBr) : 3235(OH), 1620(C=N), 1592(C=C) cm^{-1}; **^{1}HNMR ($CDCl_3$)** :- δ 1.23 (t,6H), 2.83 (q,4H), 3.95(s, 4H, 2 x CH_2), 2.35 (s, 6H, Ar-CH_3), 6.50-7.60 (m,6H), 16.05(s, 2H, -OH) ppm;. **M.S.-** *m/z* - 352 $M^{+\cdot}$

Bis(α-ethyl-2-hydroxy-4-methyl)benzylidene-1,2-ethylene diamine (3f) :-
IR (KBr) : 3195(OH), 1625(C=N), 1590(C=C) cm^{-1}; **^{1}HNMR ($CDCl_3$)** :- δ 1.22 (t,6H), 2.82 (q,4H), 3.95(s, 4H, 2 x CH_2), 2.33 (s, 6H, Ar-CH_3), 6.50-7.60 (m,6H), 15.92(s, 2H, -OH) ppm;. **M.S.-** *m/z* - 352 $M^{+\cdot}$

Bis(α-ethyl-2-hydroxy-3,5-diiodo-4-methyl)benzylidene-1,2-ethylene diamine (3g) :-
IR (KBr) : 3195(OH), 1620(C=N), 1580(C=C) cm^{-1}; **^{1}HNMR ($CDCl_3$)** :- δ 1.24 (t,6H), 3.05 (q,4H), 4.00(s, 4H, 2 x CH_2), 2.35 (s, 6H, Ar-CH_3), 6.90-7.90 (m,2H), 16.02(s, 2H, -OH) ppm;. **M.S.-** *m/z* - 856 $M^{+\cdot}$

Bis(α-ethyl-2-hydroxy-3-iodo-5-chloro)benzylidene-1,2-ethylene diamine (3h) :-
IR (KBr) : 3133(OH), 1631(C=N), 1582(C=C) cm^{-1}; **^{1}HNMR ($CDCl_3$)** :- δ 1.23 (t,6H), 3.05 (q,4H),3.93(s,4H,2 x CH_2), 7.50-8.10 (m, 4H), 16.23(s, 2H, -OH) ppm; **M.S.-** *m/z* - 645 $M^{+\cdot}$

Bis(α-ethyl-2-hydroxy-3-iodo-5-methyl)benzylidene-1,2-ethylene diamine (3i) :-
IR (KBr) : 2979(OH), 1604(C=N), 1479(C=C) cm^{-1}; **^{1}HNMR ($CDCl_3$)** :- δ 1.24 (t,6H), 2.85 (q,4H), 2.28 (s, 6H, Ar-CH_3), 4.01(s, 4H, 2 x CH_2), 6.64-7.50 (m,4H) 16.15(s, 2H, -OH) ppm; **M.S.-** *m/z* - 604 $M^{+\cdot}$

Bis(α-ethyl-2-hydroxy-3-chloro-5-iodo)benzylidene-1,2-ethylene diamine (3j) :-
IR (KBr) : 3120(OH), 1625(C=N), 1575(C=C) cm^{-1}; **^{1}HNMR ($CDCl_3$)** :- δ 1.25 (t,6H), 3.00 (q,4H), 4.00(s, 4H, 2 x CH_2), 7.50-8.10(m,4H) 16.20(s, 2H, -OH) ppm; **M.S.-** *m/z* - 645 $M^{+\cdot}$

Bis(α-ethyl-2-hydroxy-3-methyl-5-iodo)benzylidene-1,2-ethylene diamine (3k) :-
IR (KBr) : 3190(OH), 1620(C=N), 1550(C=C); $cm^{-1;}$ **^{1}HNMR ($CDCl_3$)** :- δ 1.21 (t,6H), 2.85 (q,4H), 2.30 (s,6H, Ar-CH_3), 4.00 (s,4H, 2 x CH_2), 6.60-7.55(m,4H) 16.10(s, 2H, -OH) ppm; **M.S. -** *m/z* - 604 $M^{+.}$

Antibacterial 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 18hrs. This gave an optimum growth of the test bacteria. Each purified compound was dissolved in DMSO to get desired concentration, add desired concentration of Compound (100 µg/ml) 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 are measured. It is observed that all compounds show moderate to potent antibacterial activities against gram positive and gram negative bacteria as shown in Table 2

Table 2 : Antibacterial activity of Bis-ketimines

Sr. No	Comp.	Zone of Inhibition (mm)			
		S. Aureus	*B. Subtilis*	*E.coli*	*P.auregenosa*
1	3a	02	12	14	-ve
2	3b	04	30	32	04
3	3c	02	18	20	02
4	3d	04	22	24	04
5	3e	02	14	16	-ve
6	3f	02	12	12	02
7	3g	04	12	12	04
8	3h	12	24	20	04
9	3i	08	20	10	04
10	3j	02	14	12	02
11	3k	-ve	10	10	-ve
12	Vancomycine	18	30	30	18

RESULTS AND DISCUSSION

The novel bis-ketimines were synthesized by classical as well as microwave irradiation method. Table - 1 shows comparative yields which reveals that microwave irradiation method under solvent free condition reduces time of reaction completion and improves yield of products (5-30 sec. and 83-91%) than classical method (1200-2400 sec. and 68-75%). All the synthesized compounds were characterized by IR, ^{1}HNMR, Mass data. Synthesized compounds were consistent with their chemical structures.

Assignments of chosen characteristic of IR band positions provided significant sign for the formation of the ketimines. Synthesized imines shows absorption at 1604-1631 cm^{-1} for C=N moiety confirms condensation of carbonyl with amino group which was supported by the absence of absorption band at 1700–1750 cm^{-1}. The band around 1479-1592cm^{-1} is due to C=C aromatic stretch, absorption at 2979-3235 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. A common signal appeared at δ 1.20-1.25 (t,6H), and quartet at δ 2.80-3.05 for C-CH_2 integrating two protons. The appearance of multiplets at δ 6.50–8.10 was due to aromatic protons. Another common signal appearing at δ 15.92-16.23 indicated chelation between nitrogen of C=N and hydrogen of 2-OH group in all the products. The mass spectra of the synthesized compounds show the parent peak confirming the molecular weight of the compounds.

Antibacterial activity- The data reported in Table 2 revealed that eleven compounds tested for their antibacterial activity against gram positive and gram negative bacteria. It was observed that compound 3b indicated extremely significant activity against *B. subtilis* and *E. coli* compared to control. Some compounds indicated significant activity against *B. subtilis, S. Aureus* and *E. coli* compared to control.

CONCLUSION

Novel bis-ketimines were synthesized using classical method as well as microwave assisted solvent free condition method. Microwave irradiation solvent free conditions provide advantages such as shorter reaction time, 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* . It was observed that compound 3b is most active against *E.Coli* and *B.subtilis.* Compounds 3d, 3h and 3i indicated good activity against almost all bacteria's, while remaining compounds point out moderate to poor antibacterial activities. The results signified our ketimines are capable of inhibiting the growth of bacteria to a good to moderate extent and acts as potent antibacterial agents.

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