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Studies on Synthesis of Aromatic Schiff Bases: Part-II. Synthesis, Characterization and Biological Evaluation of Ketimines from Benzophenone with Substituted-anilines

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Abstract: Ketimine were prepared from Benzophenone and Aniline, o-, m- and p-Nitroanilines using toluene as solvent by reflux method using Dean and Stark, conventional method. The compounds formed were confirmed by elemental analysis and spectral information. Also their biological activity was studied and the results were compared with standard drug, Fluconazole.

Key Words: Benzophenone, Schiff Bases, Conventional method, Dean and Stark Apparatus, Ketimines, Thin layer chromatography, UV-Vis and FTIR spectra and Biological activity.

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INTRODUCTION

Literature survey indicates that diphenylketimine is the first schiff of Benzophenones, which may be prepared by the addition of phenylmagnesium bromide to benzonitrile followed by hydrolysis with MeOH or by reaction of benzophenone with ammonia [1]. It is the reaction for study of protection of primary amines. The preparation and characterization of some transition metal complexes with new schiff base ligand derived from benzophenone was reported [2]. Many complexes of benzophenone derivatives as ligand have been prepared and studied. The complexes of VO(IV), Ni(II) and Cu(II) ions with a Schiff base derived from 2-hydroxy-4-methoxy benzophenone and benzoyl acetone have been prepared and investigated using different chemical techniques, such as; elemental analysis, conductance, magnetic, infrared and electronic spectral measurements[3]. The biological activity of Schiff bases derived from benzophenone has been widely studied such as cytotoxic activities against human oral squarnous carcinoma cells [4]. Recently we have reported the study on synthesis of ketimines from o-hydroxy-acetophenone with aniline derivatives [5].

G. Fareed *et. al.*, [6] Have studied the antioxidant potential of the schiff bases containing benzophenone moiety. Schiff bases have excellent features and structural similarities among these reagents. The facile method of preparation and synthetic simplicity of imines enables to design suitable structural properties [7-8].

In coordination chemistry, azomethine moiety form complexes with a variety of metals [9-10]. Imines have broad applications as organic intermediates for the preparation of pharmaceutical, or rubber additives [11] and protecting agent for amino group in organic synthesis [12]. They have also used as liquid crystals [13] and in polymer chemistry [14]. Schiff bases have broad applications in biological field including enzyme inhibitors [15], antitumor [16], antioxidant [17], anticancer activity [18] antimalarial[19],antibacterial[20-22], anticonvulsant [23] and antiproliferative [24].

Here in this paper we report the synthesis of ketimines from benzophenone. All the synthesized compounds were screened for their antifungal activity. Further, structures of the synthesized compounds were confirmed by elemental analysis and spectral studies. The compounds synthesized are shown in **Scheme-1**.

MATERIALS AND METHODS:

Experimental: All the starting chemicals and reagents were of synthetic and analytical grades (Sigma and Aldrich make) and used without further purification. The distilled water and the solvents including ethanol were used as received. The fungal strains, *Candida albicans* (NCIM 3471) and *Aspergillus niger* (NCIM 1196) were purchased from NCL, Pune.

General Method for Synthesis of Ketimines by using Dean Stark Apparatus: A mixture of Benzophenone and aniline or substituted aniline(1 mM each) in 30 ml toluene and a reflux condenser is attached to the flask along with the Dean Stark Apparatus to collect the water formed during the reaction progress. The reaction is subjected to the reflux in an oil bath. It took about five to six hours for the completion of process. The reaction progress is marked by the amount of water formed during the reaction and collected in the dean and stark apparatus. Also, the reaction progress is monitored by TLC (thin layer chromatography) technique, presence of new spot and absence of aniline or substituted aniline primarily indicated formation of a new compound. After completion of reaction, about 60 % of the solvent was stripped off and reaction mass is cooled, and product formed is filtered and washed by cold alcohol. It was then purified by recrystallization from suitable solvent.

The purity of the compounds formed was checked routinely by TLC(0.5 mm thickness) using silica gel G 60 F_{254} coated aluminum plates(Merck) and the obtained spots were visualized by exposing the dried plates in iodine chamber(100 ml capacity glass jar covered with glass plate) prepared using microwave oven. The micro analysis such as physical constant viz. m.p. range, colour and yield the micro-analytical data was recorded. The melting point range is determined by Digital m. p. apparatus of Equip-tronics make, Model EQ-730.

Spectral Characterization: UV-Vis spectra in nm were recorded on Schmadzu UV-1800 Model using spectroscopic grade ethanol as solvent using quartz cuvettes. The FT-IR spectra were recorded on Schmadzu spectrophotometer, Model Affinity-1, at M. J. College, Jalgaon.

Antifungal Activity Testing: The antifungal activities of the ketimines synthesized were tested in vitro for growth inhibitory against *Candida albicans* (NCIM 3471) and *Aspergillus niger* (NCIM 1196) by agar well diffusion method at different concentrations compared with Fluconazole as the positive control[25, 26] and DMSO as negative control.

RESULTS AND DISCUSSION:

The benzophenone and varied anilines were condensed to form ketimines, as per the **Scheme-1**. The physical and analytical data such as physical constant viz. M.P. range, colour and yield, for the studied ketimines was calculated and depicted in **Table-1**. The M.P. range for all the ketimines were determined by and are uncorrected

Spectral Characterization: The stock solution of the ketimines was prepared in alcohol to record the UV-Vis spectra on Schmadzu UV 1800 series spectrophotometer in the range of wavelength 600-200 nm. The representative UV-Vis spectra of the synthesized Ketimine, BPA is depicted below in **Fig. 1**. The related data of UV-Vis characteristic frequency (in nm) indicating the extent of conjugation of the groups in the molecule are indicated in the **Table-2**.

The FT-IR spectra were recorded on Schmadzu spectrophotometer, Model Affinity-1, at M. J. College, Jalgaon. The representative FTIR spectra of the synthesized Ketimine or Schiff bases, BPA is depicted below in **Fig. 2**. The related data of FTIR characteristic frequency (in cm^{-1}) of the groups indicated in the **Table-2**.

From UV data of synthesized ketimines first two bands were in the wave length (λ_{max}) range 239-290 nm 239-290 and 251.0-310.0 nm having absorption in the range 0.275 - 3.600 and 0.450 - 2.210 respectively, which are due to $\pi \rightarrow \pi^*$ transition of aromatic ring and third band, appeared in the range 355.0 - 403.0 nm having absorption in the range 0.025 - 3.260 which is likely to be due to $\pi \rightarrow \pi^*$ of -CH=N- chromophore.

The FTIR spectrum of the synthesized ketimines shows absorption in the range 2956 - 3485 cm^{-1} were assigned to □$_{>O-H}$ absorption. The appearance of new band in the range 1653-1638 cm^{-1} is accounted for the presence of-CH=N- group. No absorption at about 1700 cm^{-1}, which indicated the absence of free carbonyl group in the ketimines studied [22]. The last three compounds shows two bands in the frequency range 1399-1310 cm^{-1} and 1520 - 1445 cm^{-1} which may be attributed to the presence of -NO_2 group absorbance.

Thus, the physical and analytical data of synthesized ketimines indicated that data (viz. UV-Vis and FTIR) is in concurrence with the earlier reported [23-25] observations. From the above discussion of the analysis and discussion one arrives at the probable structures of the synthesized ketimines as depicted in **Table-3**.

Antifungal Potential: The biological activity was studied employing the antifungal method, using strains like *C. albicans* and *A. niger*. Results were compared with standard drug (Fluconazole). The results are depicted in **Table-4.**

Glimpses of in-vitro Antifungal activity of synthesized Ketimines:

- Ketimines were active against both strains *C. albicans* and *A. niger* and shows less antifungal activity than standard drug.
- The antifungal activity shown by all ketimines is directly proportional to their concentration
- Ketimine or Schiff base BP3NA is more active against both the studied strains, *C. albicans* and *A. niger.*
- All the marked activity coefficients for the studied compounds are moderate to less than the standard drug, Fluconazole.

CONCLUSION:

The present study reports the successful synthesis and antifungal activity of Ketimines or Schiff base compounds. The observed antifungal activity of all the compounds have been studied which may be due to the >C=N- linkage of the ketimines. The results of antifungal activity discussed and are compared with that of the standard drug compound, Fluconazole.

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Table 1: The Physical and analytical data for synthesized Ketimines derived from Benzophenone.

Product Code	Aniline	Mol. Wt of Product/ Colour	Mol. for.	Product Wt., gm	m. p. range, □C.	% yield*
BPA	Aniline	257/ pale yellow	$C_{19}H_{15}N$	1.83	112-113	71.21
BP2NA	2-Nitro Aniline	302/ yellow	$C_{19}H_{10}N_2O_2$	2.29	45 - 46**	75.83
BP3NA	3-Nitro Aniline	302/ yellow	$C_{19}H_{10}N_2O_2$	1.87	101-103	61.92
BP4NA	4-Nitro Aniline	302/ yellow	$C_{19}H_{10}N_2O_2$	2.65	139-141	87.75

*** isolated **m. p. seem to be lower.**

Table. 2: UV-Vis and FTIR Spectral data for Ketimines derived from Benzophenone.

I.D. of Comp.	UV max, (Absorbance)	IR Frequencies, cm^{-1}				
		$\nu_{>C=N-}$	ν_{-OH}	$\nu_{Ar-C=C<}$	ν_{-NO2}	*
BPA	355.0(0.025) 252.0 (2.884)	1653	3400	1520 1589	-	-
BP2NA	403.5(0.510) 251.0(2.212) 242.0(2.340)	1638	3475	1560 1610	1399	1510
BP3NA	374.0(0.340) 275.0sh(0.750) 239.5(3.600)	1641, 1635	2956, 3440	1543-1622	1325	1520
BP4NA	368.5(3.260) 310.0sh(0.450) 290.0(0.275)	1640	3485	1560 1593	1310	1445

sh = shoulder; * 2nd frequency due to -NO_2 gr.

Table-3: The Structural Representation with Name of the newly synthesized Ketimines.

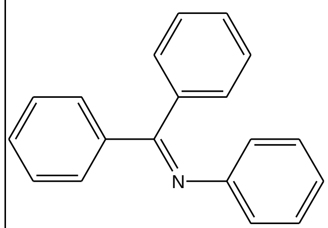
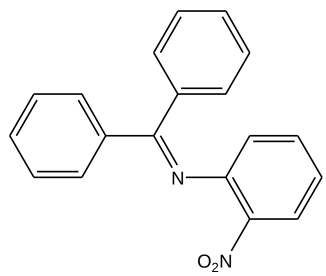
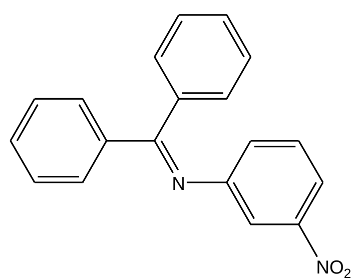
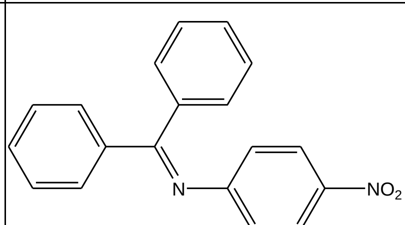
ID	Structure of Ketimine ID with Name
BPA	 N-(Diphenylmethylene)benzenamine, BPA
BP2NA	 Benzhydrylidene-(2-nitro-phenyl)-amine, BP2NA
BP3NA	 Benzhydrylidene-(3-nitro-phenyl)-amine, BP3NA
BP4NA	 Benzhydrylidene-(4-nitro-phenyl)-amine, BP4NA

Table-4: The inhibition (mm) after two days at 50 μg/ml and 100 μg/ml concentration for the studied Ketimines.

Compound I. D.	*C. albicans,* (NCIM 3471)		*A. niger,* (NCIM 1196)	
	50 μg/ml	100 μg/ml	50 μg/ml	100 μg/ml
BPA	08	09	07	09
BP2NA	06	07	08	09
BP3NA	09	12	10	12
BP4NA	08	10	09	11
DMSO	- ve	- ve	- ve	- ve
Fluconazole, (Standard Drug, +ve control)	18	21	16	18

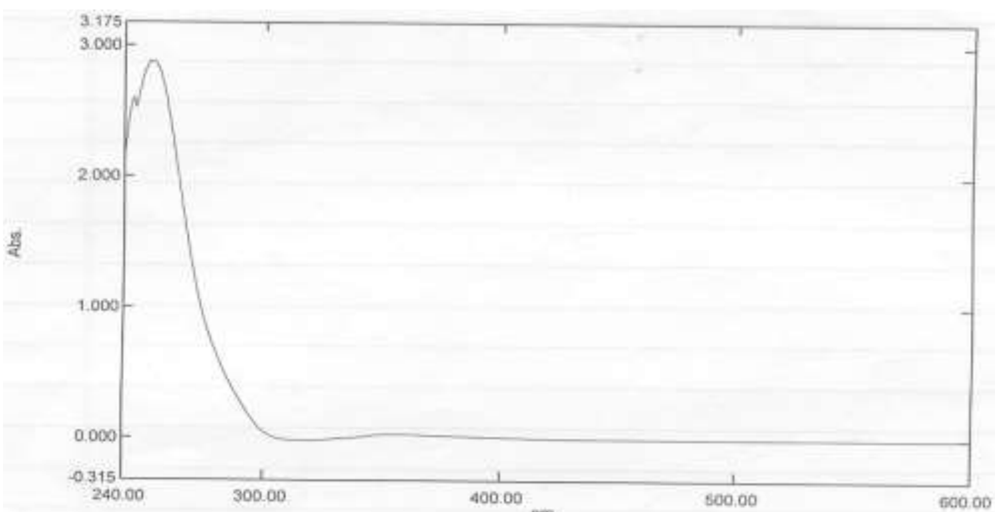


Fig. **1:** The Representative UV-Vis spectra of the synthesized Ketimines, **BPA.**

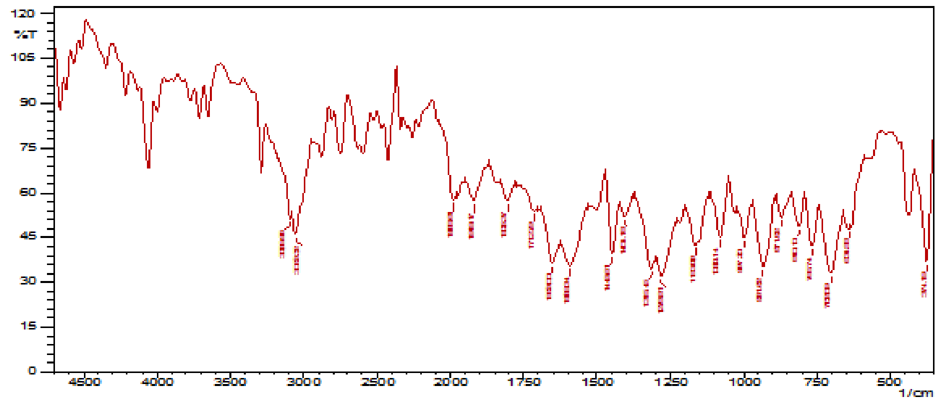
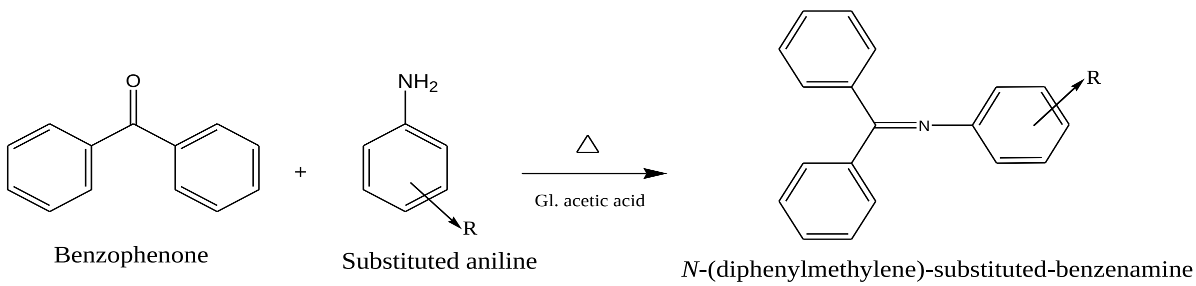


Fig. 2: The Representative FTIR spectra of the synthesized Ketimines, BPA.

Scheme-1



R- = -H(BPA); -2-NO_2(BP**2NA**); -3-NO_2(BP**3NA**) and 4-NO_2(BP**4NA**).

Scheme-1

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