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Journal of Chemical and Pharmaceutical Research, 2012, 4(1):14-17

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis of novel Schiff bases of 4-hydroxy-3-methoxy-5-nitrobenzaldehyde and Development of HPLC Chromatographic Method for their analysis

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ABSTRACT

*Vaniline [**1**] is nitrated by using known literature method to 4-hydroxy-3-methoxy-5-nitrobenzaldehyde [**2**]. The haloanilines [**3a-g**] used for the synthesis of Schiff bases was synthesized by known literature methods and by referring Vogel's Practical Organic Chemistry, 5th Edition. The nitrovaniline is reactive towards amine and forming 4-{(E)-[(4-aryl)imine]methyl}-2-methoxy-6-nitrophenol **[4a-g]**. The final compounds 4-{(E)-[(4-aryl)imine]methyl}-2-methoxy-6-nitrophenol [**4a-g**] along with starting impurities are subjected to HPLC analysis.*

Key Words: 4-hydroxy-3-methoxy-5-nitrobenzaldehyde, Haloanilines, Schiff Bsaes, nitrovaniline, HPLC.

INTRODUCTION

The compounds containing azomethine (-C=N-) group are know as Schiff bases, are formed by the condensation of a primary amines with a carbonyl compounds such as aldehydes or ketones. Schiff bases are characterized by the –N=CH– (imine) group which is important in elucidating the mechanism of transamination and racemisation reactions in biological systems.[1,2] They have been synthesized from a variety of compounds, such as amino thiazoles, 2-hydroxy-1-napthalaniline, amino sugars, aromatic aldehydes, isatin, the triazole ring, thiosemicarbazides, amino acids, pyrazolone, *etc.*[3–7] Literature survey shows that Schiff bases show bacteriostatic and bactericidal activity.[8] Antibacterial, antifungal, antitumor, anticancer activity has been reported and they are also active against a wide range of organisms, *e.g. C. albicans, E. coli, S. aureus, B. polymyxa, P. viticola, etc.*[9-11] Schiff bases containing *o*-vanillin possesses antifungal, antibacterial properties [12] and it acts as a weak inhibitor of tyrosinase, display both antimutagenic and comutagenic properties in *Escherichia coli*[13] . Schiff bases are plays very important role in many biological and chemical reactions; because of the imine linkage. Imines are possess antibacterial and more antifungal activities. Schiff bases (Lei wang et.al.) are the important compounds owing to their wide range of biological activities and Industrial applications. They have been found to possess the pharmacological activities such as antimalarial (Li et. al., 2003), anticancer (Villar et. al., 2004), antibacterial (Venugopal et. al., 2008), antifungal (Pandey, et. al., 2003), antitubercular (Bhat et. al., 2005), antiinflammetery, antimicrobial (Wadher et. al., 2009) and antiviral (Karthikeyan et. al., 2006), etc. M S Suresh and V Prakash et.al[14]. (2010), synthesized and characterized Schiff bases[15] of vanillin and 4-aminoantipyrane and their transition metal complexes and study their antimicrobial activities. The Schiff base and its complexes show good antibacterial properties. K Siddappa, M Mallikarjun[16] et.al. (2008), shows that Schiff system of vanillin and PDAB is used for the spectrophotometric determination of metronidazole.

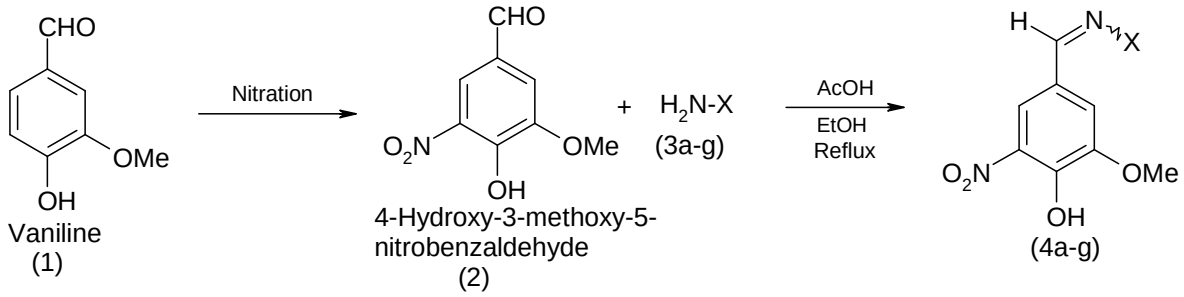
A rapid, sensitive and specific RP-HPLC method[17] involving UV detection was developed and validated for the determination and quantification of 4-{(E)-[(4-aryl)imine]methyl}-2-methoxy-6-nitrophenol [**4a-g]**. Chromatography was carried out on Waters 2695 separation module HPLC system with Waters 2487 Dual wavelength Absorbance detector and Waters 2998 Photodiode Array Detector using Stainles Steel Column of dimension 15 cm x 4.6 mm packed with octadecylsilane bonded with silica (Make : Phenomenex Prodigy 5 µ ODS 3 100A column is suitable) using filtered and degassed mixture of Buffer (prepared by addition of 1 L purified water and 10 ml of acetic acid and 5 ml Triethylamine) and suitable mobile phases according to the solubility and nature of compounds. The mobile phase was flow of 10 ml/min and effluents was monitored at different wavelengths. The method was validated in terms of Specificity, Linearity and Range, Precision, Accuracy, Intermediated Pricision, Solution stability, and Rubustness.

In this paper we describe a simple, in expensive, sensitive and validated HPLC method for the simultaneous determination 4-{(E)-[(4-aryl)imine]methyl}-2-methoxy-6-nitrophenol [**4a-g]**.

EXPERIMENTAL SECTION

Experimental Work:

Vaniline [**1]** is nitrated by using known literature method to 4-hydroxy-3-methoxy-5-nitrobenzaldehyde [**2]**. The haloanilines [**3a-g]** used for the synthesis of Schiff bases was synthesized by known literature methods and by referring Vogel's Practical Organic Chemistry, 5th Edition. The nitrovaniline is reactive towards amine and forming 4-{(E)-[(4-aryl)imine]methyl}-2-methoxy-6-nitrophenol [**4a-g]**.

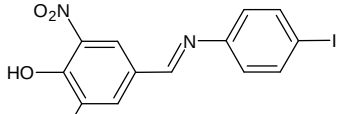
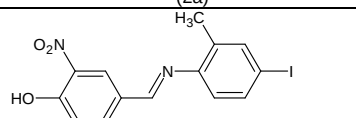


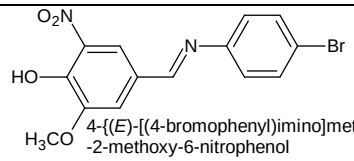
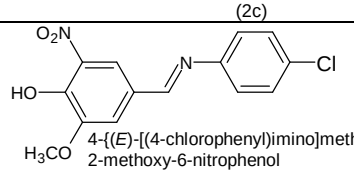
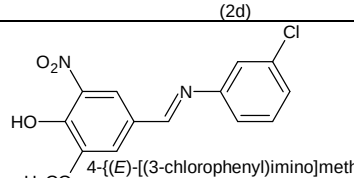
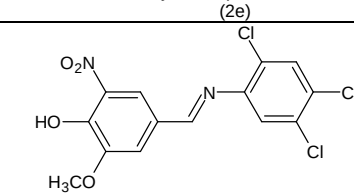
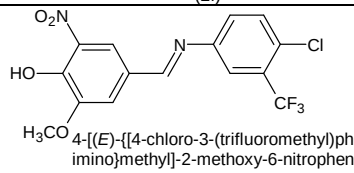
H_2N-X – 4-iodoaniline, 4-iodo-2-methylaniline, 4-bromoaniline, 4-chloroaniline, 3-chloroaniline, 2,4,5-trichloroaniline, 4-chloro-3-trifluoromethylaniline.

Synthesis of Schiff bases:

Add 200 mg of 4-hydroxy-3-methoxy-5-nitrovaniline (1.015 mmol) [**2]** in 10 ml of absolute alcohol and for few minutes till all aldehyde get dissolve. Add 1.02 mmol of haloanilines [**3a-g]** in above reaction mixture with constant stirring and finally add catalytic amount of acetic acid. Reflux the reaction mixture with stirring for about 30 – 50 minutes and check the completion of reaction with help of TLC (in pet ether and ethyl acetate). Cool the reaction mixture and filter the resulting solid 4-{(E)-[(4-aryl)imine]methyl}-2-methoxy-6-nitrophenol **[4a-g]** on Buckner funnel, wash with cold ethanol. Record the yield, M.P and recrystallized from absolute ethanol.

Table 1: Starting amines, Structure and IUPAC name of product, Yield, m.p. and NMR data of the product.

Starting Amines	Name and structure of Product	Yield	M.P. ^{0}C	NMR data (δ in ppm) in DMSO-D6 (300MHz)
4-Iodoaniline 07mm01/090811	 4-{(*E*)-[(4-iodophenyl)imino]methyl}-2-methoxy-6-nitrophenol (2a)	82%	135	**3.94 (s, 3H)**; 6.43 (d, 1H); 7.2 (dd, 2H); 7.7 (dd, 2H); 8.1 (d, 1H); **8.6 (s, 1H)**; **10.90 (bs, 1H).**
4-Iodo-2-methylaniline 07mm02/100811	 4-{(*E*)-[(4-iodo-2-methylphenyl)imino]methyl}-2-methoxy-6-nitrophenol (2b)	74%	105	2.26 (s, 3H); **3.96 (s, 3H)**; 6.87 (d, 1H); 7.55 (d, 1H); 7.62 (s, 1H); 7.60 (s, 1H); 8.01 (s, 1H); **8.46 (s, 1H)**; **10.95 (bs, 1H)**

4-Bromoaniline 07mm03/100811	 4-{(*E*)-[(4-bromophenyl)imino]methyl} -2-methoxy-6-nitrophenol (2c)	78%	145	**3.94 (s, 3H)**; 7.25 (dd, 2H); 7.61 (dd, 2H); 7.74 (s, 1H); 8.05 (s, 1H); **8.61 (s, 1H)**; **10.90 (bs, 1H)**
4-Chloroaniline 07mm04/100811	 4-{(*E*)-[(4-chlorophenyl)imino]methyl}- 2-methoxy-6-nitrophenol (2d)	81%	143	**3.94 (s, 3H)**; 7.32 (dd, 2H); 7.48 (dd, 2H); 7.75 (s, 1H); 8.05 (s, 1H); **8.61 (s, 1H)**; **10.95 (bs, 1H)**
3-Chloroaniline 07mm05/100811	 4-{(*E*)-[(3-chlorophenyl)imino]methyl}- 2-methoxy-6-nitrophenol (2e)	67%	125	**3.95 (s, 3H)**; 7.2-7.6 (m, 4H); 7.75 (s, 1H); 8.10 (s, 1H); **8.64 (s, 1H)**; **10.90 (bs, 1H)**
2,4,5-Trichloroaniline 07mm06/110811	 2-methoxy-6-nitro-4-{(*E*)-[(2,4,5-trichlorophenyl) imino]methyl}phenol (2f)	76%	142	**3.96 (s, 3H)**; 7.62 (s, 1H); 7.78 (s, 1H); 8.04 (s, 1H); 8.11 (s, 1H); **8.59 (s, 1H)**; **11.22 (bs, 1H)**
4-Chloro-3- trifluoromethyl-aniline 07mm08/190811	 4-[(*E*)-{[4-chloro-3-(trifluoromethyl)phenyl] imino}methyl]-2-methoxy-6-nitrophenol (2g)	85%	168	**3.96 (s, 3H)**; 7.60 (s, 1H); 7.73 -7.78 (m, 3H); 8.05 (s, 1H); **8.70 (s, 1H)**; **10.95 (bs, 1H)**

HPLC Characterization:

A simple, fast and cost-consious method [**18]** has been developed for the determination of all below compounds by High Pressure Liquid Chromatography. The analysis was carried out on Waters 2695 separation module HPLC system with Waters 2487 Dual wavelength Absorbance detector . The column used was a stainless steel column of dimension 15 cm x 4.6 mm , packed with octadecylsilane bonded to porous silica (Make : Waters X-terra column is suitable).The detector used was Ultraviolet (UV and Photodiodearray (PDA) detector.

The method details are as follows,
Flow rate : 1.0 ml/min Detector, Wavelength : 244 nm,
Column oven temperature : 32°C, injection volume : 10 µl
Mobile phase : Methanol : ACN : Water (42:42:20 proportions in volume), Diluent : Methanol

Apart from above mentioned method, several other methods are also tried but due to longer Retention time and Co-elution the above method is selective and specific.

The results of the HPLC analysis are as follows :

Solubility observation and % assay determined by HPLC

Compound name	Solubility in Water	Solubility in Methanol	Solubility in ACN	HPLC PURITY	Peak Purity by HPLC
4-Iodoaniline	Insoluble	Soluble	soluble	75 %	Peak is spectrally pure
4-Iodo-2-methylaniline	Insoluble	Soluble	soluble	75 %	Peak is spectrally pure
4-Bromoaniline	Insoluble	Soluble	soluble	67 %	Peak is spectrally pure
4-Chloroaniline	Insoluble	Soluble	soluble	63 %	Peak is spectrally pure
3-Chloroaniline	Insoluble	Soluble	soluble	55 %	Peak is spectrally pure
2,4,5-Trichloroaniline	Insoluble	Soluble	soluble	100 %	Peak is spectrally pure
4-Chloro-3-trifluoromethyl-aniline	Insoluble	Soluble	soluble	70 %	Peak is spectrally pure

RESULTS AND DISCUSSION

Vaniline **[1]** is nitrated by using known literature method to 4-hydroxy-3-methoxy-5-nitrobenzaldehyde [**2]**. The NMR spectra of the nitrovanillin shows δ values at 3.96 (s, 3H) is for $–OCH_3$ group protons and 11.22 (bs, 1H) is for deshielded phenolic –OH proton. The signal at 9.87 (s, 1H) is for aldehydic proton which is not observed in the final products. The nitrovaniline is reactive towards amine and forming 4-{(E)-[(4-aryl)imine]methyl}-2-methoxy-6-nitrophenol [**4a-g]**. The structures of the Schiff bases are confirmed by NMR spectra. The two signals of phenolic –OH and $–OCH_3$ protons are present in final Schiff bases NMR with slight shielding/deshielding effect depending on the aniline used for the coupling. The new peak at 8.4-8.7 ppm is due to azomethine proton confirm the formation of Schiff bases.

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